



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>5</sup> :</b>  <b>A61K 47/48</b>	<b>A2</b>	<b>(11) International Publication Number:</b> <b>WO 92/02257</b>  <b>(43) International Publication Date:</b> 20 February 1992 (20.02.92)
<b>(21) International Application Number:</b> PCT/US91/05476 <b>(22) International Filing Date:</b> 6 August 1991 (06.08.91)  <b>(30) Priority data:</b> 566,208 10 August 1990 (10.08.90) US  <b>(60) Parent Application or Grant</b> <b>(63) Related by Continuation</b> US 566,208 (CIP) Filed on 10 August 1990 (10.08.90)  <b>(71) Applicant (for all designated States except US):</b> G.D. SEARLE & CO. [US/US]; P.O. Box 5110, Chicago, IL 60680-5110 (US).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only) :</b> MANNING, Robert, E. [US/US]; 1298 South Mason Road, St. Louis, MO 63131 (US). REITZ, David, B. [US/US]; 14814 Pleasant Ridge Court, Chesterfield, MO 63017 (US).		<b>(74) Agents:</b> KEANE, J., Timothy et al.; G.D. Searle & Co., Corporate Patent Department, P.O. Box 5110, Chicago, IL 60680-5110 (US).  <b>(81) Designated States:</b> AT, AT (European patent), AU, BB, BE (European patent), BF (OAPI patent), BG, BJ (OAPI patent), BR, CA, CF (OAPI patent), CG (OAPI patent), CH, CH (European patent), CI (OAPI patent), CM (OAPI patent), CS, DE, DE (European patent), DK, DK (European patent), ES, ES (European patent), FI, FR (European patent), GA (OAPI patent), GB, GB (European patent), GN (OAPI patent), GR (European patent), HU, IT (European patent), JP, KP, KR, LK, LU, LU (European patent), MC, MG, ML (OAPI patent), MN, MR (OAPI patent), MW, NL, NL (European patent), NO, PL, RO, SD, SE, SE (European patent), SN + (OAPI patent), SU, TD (OAPI patent), TG (OAPI patent), US.  <b>Published</b> <i>Without international search report and to be republished upon receipt of that report.</i>
<b>(54) Title:</b> RENAL-SELECTIVE ANGIOTENSIN II ANTAGONISTS FOR TREATMENT OF HYPERTENSION  <div style="text-align: center;"> </div>		
<b>(57) Abstract</b>  <p>Renal-selective compounds are described which, in one embodiment, are prodrugs preferentially converted in the kidney to compounds capable of blocking angiotensin II (AII) receptors. These prodrugs are conjugates formed from two components, namely, a first component provided by an AII antagonist compound and a second component which is capable of being cleaved from the first component when both components are chemically linked within the conjugate. The two components are chemically linked by a bond which is cleaved selectively in the kidney, for example, by an enzyme. The liberated AII antagonist compound is then available to block AII receptors within the kidney. Conjugates of particular interest are glutamyl derivatives of biphenylmethyl 1H-substituted imidazole compounds, of which N-acetyl-L-glutamic acid, 5-[[4'-[2-butyl-4-chloro-5-(hydroxymethyl)-1H-imidazol-1-ylmethyl] [1,1'-biphenyl]-2-yl]carbonyl]hydrazide shown above is an example.</p>		

# + DESIGNATIONS OF "SU"

It is not yet known for which States of the former Soviet Union any designation of the Soviet Union has effect.

## *FOR THE PURPOSES OF INFORMATION ONLY*

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	ES	Spain	MG	Madagascar
AU	Australia	FI	Finland	ML	Mali
BB	Barbados	FR	France	MN	Mongolia
BE	Belgium	GA	Gabon	MR	Mauritania
BF	Burkina Faso	GB	United Kingdom	MW	Malawi
BG	Bulgaria	GN	Guinea	NL	Netherlands
BJ	Benin	GR	Greece	NO	Norway
BR	Brazil	HU	Hungary	PL	Poland
CA	Canada	IT	Italy	RO	Romania
CF	Central African Republic	JP	Japan	SD	Sudan
CG	Congo	KP	Democratic People's Republic of Korea	SE	Sweden
CH	Switzerland	KR	Republic of Korea	SN	Senegal
CI	Côte d'Ivoire	LI	Liechtenstein	SU <sup>+</sup>	Soviet Union
CM	Cameroon	LK	Sri Lanka	TD	Chad
CS	Czechoslovakia	LU	Luxembourg	TG	Togo
DE	Germany	MC	Monaco	US	United States of America
DK	Denmark				

**RENAL-SELECTIVE ANGIOTENSIN II ANTAGONISTS FOR  
TREATMENT OF HYPERTENSION**

**Field of the Invention**

5

This invention is in the field of cardiovascular therapeutics and relates to a class of compounds useful in control of hypertension. Of particular interest is a class of prodrugs of angiotensin II antagonists which, when selectively  
10 hydrolyzed in the kidney, provide hypertension control.

**Background of the Invention**

The renin-angiotensin system is one of the hormonal  
15 mechanisms involved in regulation of pressure/volume homeostasis and in expression of hypertension. Activation of the renin-angiotensin cascade begins with renin secretion from the juxtaglomerular apparatus of the kidney and culminates in the formation of angiotensin II, an octapeptide which is the  
20 primary active species of this system. Angiotensin II is a potent vasoconstrictor agent and also produces other physiological effects such as promoting aldosterone secretion, promoting sodium and fluid retention, inhibiting renin secretion, increasing sympathetic nervous system activity,  
25 increasing vasopressin secretion, causing positive cardiac inotropic effect and modulating other hormonal systems.

Previous studies have shown that antagonizing angiotensin II at its receptors is a viable approach to  
30 inhibit the renin-angiotensin system, given the pivotal role of this octapeptide which mediates the actions of the renin-angiotensin system through interaction with various tissue receptors. There are several known angiotensin II antagonists, most of which are peptidic in nature. Such  
35 peptidic compounds are of limited use due to their lack of

oral bioavailability or their short duration of action. Also, commercially-available peptidic angiotensin II antagonists (e.g., Saralasin) have a significant residual agonist activity which further limit their therapeutic application.

5

Non-peptidic compounds with angiotensin II antagonist properties are known. For example, the sodium salt of 2-n-butyl-4-chloro-1-(2-chlorobenzyl)imidazole-5-acetic acid has specific competitive angiotensin II antagonist activity as shown in a series of binding experiments, functional assays and in vivo tests [P. C. Wong et al, J. Pharmacol. Exp. Ther., 247 (1), 1-7 (1988)]. Also, the sodium salt of 2-butyl-4-chloro-1-(2-nitrobenzyl)imidazole-5-acetic acid has specific competitive angiotensin II antagonist activity as shown in a series of binding experiments, functional assays and in vivo tests [A. T. Chiu et al, European J. Pharmacol., 157, 3121 (1988)]. A family of 1-benzylimidazole-5-acetate derivatives has been shown to have competitive angiotensin II antagonist properties [A. T. Chiu et al, J. Pharmacol. Exp. Ther., 250 (3), 867-874 (1989)]. U.S. Patent No. 4,816,463 to Blankey et al describes a family of 4,5,6,7-tetrahydro-1H-imidazo(4,5-c)-tetrahydro-pyridine derivatives useful as antihypertensives, some of which are reported to antagonize the binding of labelled angiotensin II to rat adrenal receptor preparation and thus cause a significant decrease in mean arterial blood pressure in conscious hypertensive rats. EP No. 253,310, published 20 January 1988, describes a series of aralkyl imidazole compounds, including in particular a family of biphenylmethyl substituted imidazoles, as antagonists to the angiotensin II receptor. EP No. 323,841 published 12 July 1989 describes four classes of angiotensin II antagonists, namely, biphenylmethylpyrroles, biphenylmethylpyrazoles, biphenylmethyl-1,2,3-triazoles and biphenylmethyl 4-substituted-4H-1,2,4-triazoles, including the compound 3,5-



dibutyl-4-[(2'-carboxybiphenyl-4-yl)methyl]-4H-1,2,4-triazole.  
U.S. Patent No. 4,880,804 to Carini et al describes a family  
of biphenylmethylbenzimidazole compounds as angiotensin II  
receptor blockers for use in treatment of hypertension and  
5 congestive heart failure.

One disadvantage of these angiotensin II antagonist  
compounds is that the desired hypertension-reducing effect may  
be offset by hypotension-induced compensatory stimulation of  
10 the renin-angiotensin system or stimulation of the sympathetic  
nervous system, either of which may result in promotion of  
sodium and water retention. Also, some angiotensin II  
antagonists may have toxicological effects systemically which  
precludes their use at doses necessary to be effective in  
15 reducing blood pressure.

To avoid such systemic side effects, drugs may be  
targetted to the kidney by creating a conjugate compound that  
would be a renal-specific prodrug containing the targetted  
20 drug modified with a chemical carrier moiety. Cleavage of the  
drug from the carrier moiety by enzymes predominantly  
localized in the kidney releases the drug in the kidney. Gamma  
glutamyl transpeptidase and acylase are examples of such  
cleaving enzymes found in the kidney which have been used to  
25 cleave a targetted drug from its prodrug carrier within the  
kidney.

Renal targetted prodrugs are known for delivery of  
a drug selectively to the kidney. For example, the compound L-  
30  $\gamma$ -glutamyl amide of dopamine when administered to dogs was  
reported to generate dopamine in vivo by specific enzymatic  
cleavage by  $\gamma$ -glutamyl transpeptidase [J. J. Kyncl et al, Adv.  
Biosc., 20, 369-380 (1979)]. In another study,  $\gamma$ -glutamyl and  
N-acyl- $\gamma$ -glutamyl derivatives of the anti-bacterial compound  
35 sulfamethoxazole were shown to deliver relatively high

concentrations of sulfamethoxazole to the kidney which involved enzymatic cleavage of the prodrug by acylamino acid deacylase and  $\gamma$ -glutamyl transpeptidase [M. Orlowski et al, J. Pharmacol. Exp. Ther., 212, 167-172 (1980)]. The N- $\gamma$ -  
5 glutamyl derivatives of 2-, 3-, or 4-aminophenol and p-fluoro-L-phenylalanine have been found to be readily solvolyzed in vitro by  $\gamma$ -glutamyl transpeptidase [S.D.J. Magnan et al, J. Med. Chem., 25, 1018-1021 (1982)]. The hydralazine-like vasodilator 2-hydrazino-5-n-butylpyridine (which stimulates  
10 guanylate cyclase activity) when substituted with the N-acetyl- $\gamma$ -glutamyl residue resulted in a prodrug which provided selective renal vasodilation [K. G. Hofbauer et al, J. Pharmacol. Exp. Ther., 212, 838-844 (1985)]. The dopamine prodrug  $\gamma$ -L-glutamyl-L-dopa ("gludopa") has been shown to be  
15 relatively specific for the kidney and to increase renal blood flow, glomerular filtration and urinary sodium excretion in normal subjects [D. P. Worth et al, Clin. Sci., 69, 207-214 (1985)]. In another study, gludopa was reported to be an effective renal dopamine prodrug whose activity can be blocked  
20 by the dopa-decarboxylase inhibitor carbidopa [R. F. Jeffrey et al, Br. J. Clin. Pharmac., 25, 195-201 (1988)]. A class of 4-ureido derivatives of isoquinolin-3-ol has been investigated for renal specific effects such as increases in renal vasodilation and renal blood flow [R. M. Kanojia et al, J.  
25 Med. Chem., 32, 990-997 (1989)].

#### BRIEF DESCRIPTION OF THE DRAWING FIGURES

30 Fig. 1 is a graph showing reduction in mean arterial pressure by intravenous administration of a conjugate of the invention to a spontaneously hypertensive rat.

Fig. 2 is a graph showing angiotensin II pressor  
35 response in a spontaneously hypertensive rat infused by

intravenous administration with a conjugate of the invention over a period of three days.

Fig. 3 is a graph showing urinary sodium excretion response to angiotensin II infusion in conscious normotensive rats followed by administration of a saline vehicle, an angiotensin II antagonist, or a renal-selective conjugate of the invention.

Fig. 4 is a graph showing mean arterial pressure response to angiotensin II infusion in conscious normotensive rats followed by administration of a saline vehicle, an angiotensin II antagonist, or a renal-selective conjugate of the invention..

#### DESCRIPTION OF THE INVENTION

Treatment of chronic hypertension or sodium-retaining disorders such as congestive heart failure, cirrhosis and nephrosis, may be accomplished by administering to a susceptible or afflicted subject a therapeutically-effective amount of a renal-selective prodrug capable of causing blood-pressure reducing effects by selective action in the kidney. An advantage of such renal-selective prodrug therapy resides in reduction or avoidance of adverse side effects associated with systemically-acting drugs.

Advantages of a renal-selective antihypertensive compound are several. First, the renal-selective compound is targetted at those pathophysiological mechanisms which occur primarily in the kidney. Second, the regulation of other organ systems is unaffected; thus, normal physiological regulation of other organ systems is maintained. Third, fewer side-effects may be anticipated, since the compound remains

inactive until cleaved in the kidneys. Similarly, fewer negative drug-drug interactions may be anticipated. Finally, since a renal-selective accumulation of active compound may occur, which is not dependent on plasma levels of the parent  
5 compound, lower doses of the renal-selective compound compared to active parent compound may be used.

A renal-selective prodrug is provided by a conjugate comprising a residue of an angiotensin II antagonist  
10 compound, which conjugate is renal selective. The conjugate will typically comprise a first component and a second component connected together by a cleavable or hydrolyzable bond. The term "renal-selective", as used to characterize a conjugate of the invention, embraces any of the following four  
15 pharmacological events: (1) the conjugate is selectively taken up by the kidney and is selectively cleaved in the kidney; (2) the conjugate is not taken up selectively by the kidney, but is selectively cleaved in the kidney; (3) the conjugate is selectively taken up by the kidney and then  
20 cleaved in the kidney; or (4) where the conjugate itself is active as an angiotensin II antagonist, the conjugate is selectively taken up by the kidney without cleavage of the hydrolyzable bond.

25 The first component of a conjugate of the invention is a residue derived from an antagonist compound capable of inhibiting angiotensin II (AII) receptors, especially those AII receptors located in the kidney. The second residue is capable of being cleaved from the first residue  
30 preferentially. Cleaving of the first and second residues may be accomplished by a variety of mechanisms. For example, the bond may be cleaved by an enzyme in the kidney.

The residue providing the first component may be  
35 characterized as the "AII antagonist active" residue. Such

"active" residue may be provided by a compound having AII antagonist activity or by a metabolite of such compound having AII antagonist activity. The residue providing the second component may be characterized in being capable of forming a cleavable bond connecting the "active" first residue and the second residue. Such bond is cleavable by an enzyme located in the kidney. In a preferred embodiment, this cleavable bond is typically a hydrolyzable amide bond, that is, a bond between a carbonyl-terminated moiety and a reactive nitrogen-terminated moiety, such as an amino-terminated moiety, which may be cleaved by an enzyme found in the kidney, but which is not cleaved substantially by enzymes located in other organs or tissues of the body. Preferred bond-cleaving enzymes would be found predominantly in the kidney.

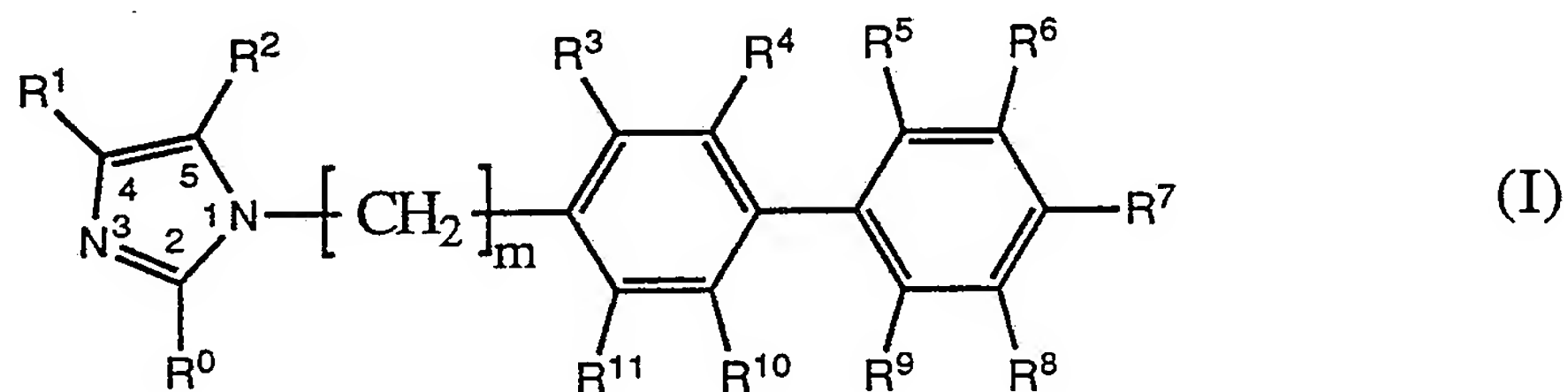
The conjugate containing the residue of an AII antagonist compound and containing the cleavable fragment or residue may possess AII antagonist activity comparable to, or more than, or less than, the AII antagonist compound which forms the conjugate. In one embodiment of the invention, the conjugate will have AII receptor blocking activity comparable to the AII antagonist component forming the conjugate. In another embodiment of the invention, the conjugate will have AII receptor blocking activity less than the AII receptor blocking activity forming the conjugate. One advantage of such differential activity between the conjugate and the AII antagonist component is that certain side effects associated with non-renal, systemic AII receptor blocking may be avoided or reduced. For example, at least one conjugate of the invention has been found to have a very large differential in AII receptor blocking activities between the conjugate and the AII antagonist component forming the conjugate. Such differential activity is advantageous in that therapeutically-effective antihypertensive doses of the conjugate may be administered to give renal-selective AII receptor blocking



action resulting from kidney-specific enzyme hydrolysis or metabolism of the conjugate to free the active AII receptor blocker within the kidney. Inasmuch as this renal-selective conjugate has relatively low AII receptor blocking activity, compared to the AII receptor compound forming the conjugate, this conjugate will have fewer adverse side effects associated with unwanted systemic interaction with non-renal AII receptors such as found in the vascular bed.

### DETAILED DESCRIPTION OF THE INVENTION

The first residue of the conjugate may be selected from any class of compounds, or metabolites thereof, having angiotensin II antagonist activity. An example of one such class of angiotensin II antagonist compounds is provided by a class of biphenylmethyl 1H-substituted-1,3-imidazole compounds defined by Formula I:

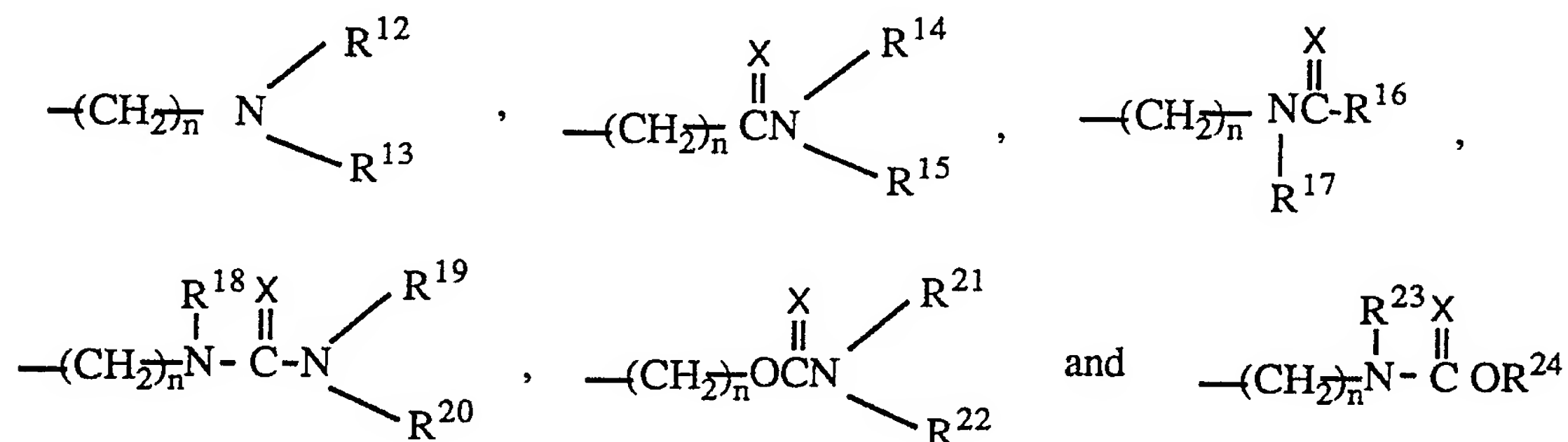


wherein m is a number selected from one to four, inclusive;

wherein each of R<sup>0</sup> through R<sup>11</sup> is independently selected from hydrido, alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, formyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkylcarbonylalkyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl,

mercaptocarbonyl, mercaptothiocarbonyl, mercaptoalkyl,  
 alkoxy carbonyloxy, alkylthio, cycloalkylthio,  
 alkylthiocarbonyl, alkylcarbonylthio, alkylthiocarbonyloxy,  
 alkylthiocarbonylthio, alkylthiothiocarbonyl,  
 5 alkylthiothiocarbonylthio, arylthio, arylthiocarbonyl,  
 arylcarbonylthio, arylthiocarbonyloxy, arylthiocarbonylthio,  
 arylthiothiocarbonyl, arylthiothiocarbonylthio, aralkylthio,  
 aralkylthiocarbonyl, aralkylcarbonylthio,  
 aralkylthiocarbonyloxy, aralkylthiocarbonylthio,  
 10 alkylthiocarbonyl, aralkylthiocarbonylthio, mercapto,  
 alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl,  
 aralkylsulfonyl, arylsulfinyl, arylsulfonyl, phthalimido,  
 phthalimidoalkyl, heteroaryl, heteroarylalkyl,  
 cycloheteroalkyl, cycloheteroalkylalkyl and  
 15 cycloheteroalkylcarbonylalkyl wherein each of said heteroaryl-  
 and cyclohetero-containing groups has one or more ring atoms  
 selected from oxygen, sulfur and nitrogen atoms, and wherein  
 each of  $R^0$  through  $R^{11}$  may be further independently selected  
 from amino and amido radicals of the formula

20



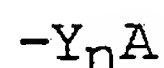
wherein X is oxygen atom or sulfur atom;

25

wherein each n is a number independently selected from zero to  
 six, inclusive;

wherein each of  $R^{12}$  through  $R^{24}$  is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl, and wherein  $R^{12}$  and  $R^{13}$  taken together,  $R^{14}$  and  $R^{15}$  taken together,  $R^{16}$  and  $R^{17}$  taken together,  $R^{19}$  and  $R^{20}$  taken together and  $R^{21}$  and  $R^{22}$  taken together may each form a heterocyclic group having five to seven ring members including the nitrogen atom of said amino or amido radical and which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms and which heterocyclic group may be saturated or partially unsaturated; wherein  $R^{12}$  and  $R^{13}$  taken together,  $R^{14}$  and  $R^{15}$  taken together,  $R^{19}$  and  $R^{20}$  taken together and  $R^{21}$  and  $R^{22}$  taken together may each form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino or amido radical and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms;

and wherein each of  $R^3$  through  $R^{11}$  may be further independently selected from hydrido and haloalkyl, and from acidic moieties of the formula

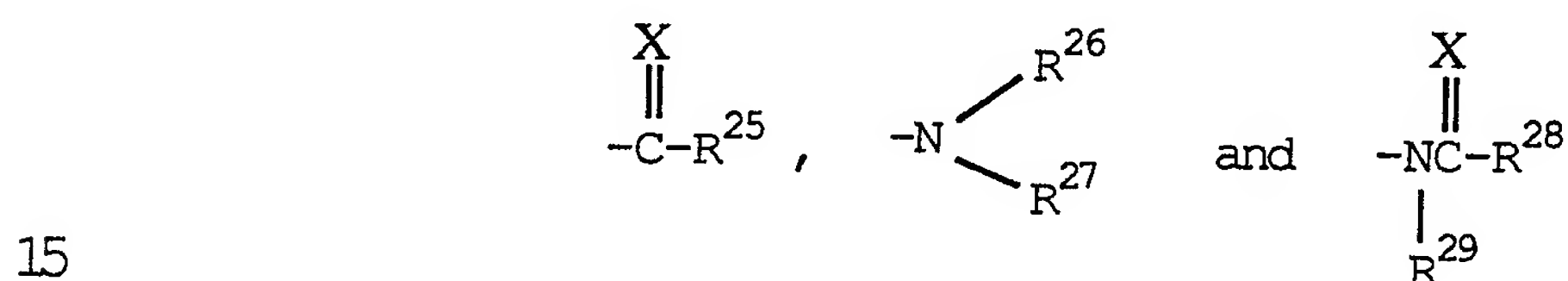


wherein  $n$  is a number selected from zero through three, inclusive, and wherein  $A$  is an acidic group selected to contain at least one acidic hydrogen atom, and the amide, ester and salt derivatives of said acidic moieties;

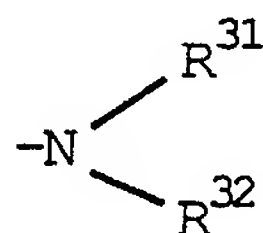
wherein  $Y$  is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aryl, aralkyl and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms;

and wherein any of the foregoing  $R^1$  through  $R^{24}$ ,  $Y$  and  $A$

groups having a substitutable position may be substituted with one or more groups selected from hydroxy, alkyl, alkenyl, alkynyl, aralkyl, hydroxyalkyl, trifluoromethyl, difluoroalkyl, oxo, alkoxy, aryloxy, aralkoxy, aralkylthio, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, aroyl, cycloalkenyl, cyano, cyanoamino, nitro, alkylcarbonyloxy, alkoxycarbonyloxy, alkylcarbonyl, alkoxycarbonyl, carboxyl, mercapto, mercaptocarbonyl, alkylthio, arylthio, alkylthiocarbonyl, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms, and amino and amido radicals of the formula

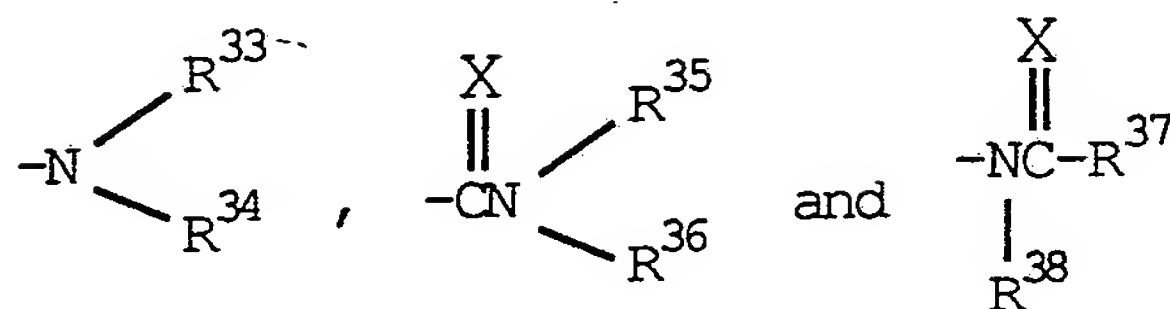


wherein X is selected from oxygen atom and sulfur atom;  
wherein R<sup>25</sup> is selected from hydrido, alkyl, cycloalkyl,  
cycloalkylalkyl, aralkyl, aryl, DR<sup>30</sup> and



wherein D is selected from oxygen atom and sulfur atom and R<sup>30</sup> is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl and aryl; wherein each of R<sup>25</sup>, R<sup>26</sup>, R<sup>27</sup>, R<sup>28</sup>, R<sup>29</sup>, R<sup>31</sup> and R<sup>32</sup> is independently selected from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, carboxyl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl, and wherein each of R<sup>26</sup>, R<sup>27</sup>, R<sup>28</sup>, R<sup>29</sup>, R<sup>31</sup> and R<sup>32</sup> is further

independently selected from amino and amido radicals of the formula



5

wherein X is oxygen atom or sulfur atom;

wherein each of R<sup>33</sup>, R<sup>34</sup>, R<sup>35</sup>, R<sup>36</sup>, R<sup>37</sup> and R<sup>38</sup> is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl, and wherein R<sup>26</sup> and R<sup>27</sup> taken together and R<sup>28</sup> and R<sup>29</sup> taken together may each form a heterocyclic group having five to seven ring members including the nitrogen atom of said amino or amido radical, which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms and which heterocyclic group may be saturated or partially unsaturated; wherein R<sup>26</sup> and R<sup>27</sup> taken together and R<sup>31</sup> and R<sup>32</sup> taken together may each form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino or amido radical and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms;

25

with the proviso that at least one of said R<sup>1</sup> through R<sup>24</sup>, Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

30



or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

Conjugates of the invention are therapeutically effective in treatment of cardiovascular disorders by acting directly, or by providing cleavable components selected from Formula I compounds which act directly, as antagonists to, or blockers of, the angiotensin II (AII) receptor. Thus, conjugates of Formula I would be therapeutically effective in treatment of cardiovascular disorders or would be precursors to, or prodrugs of, therapeutically-effective compounds.

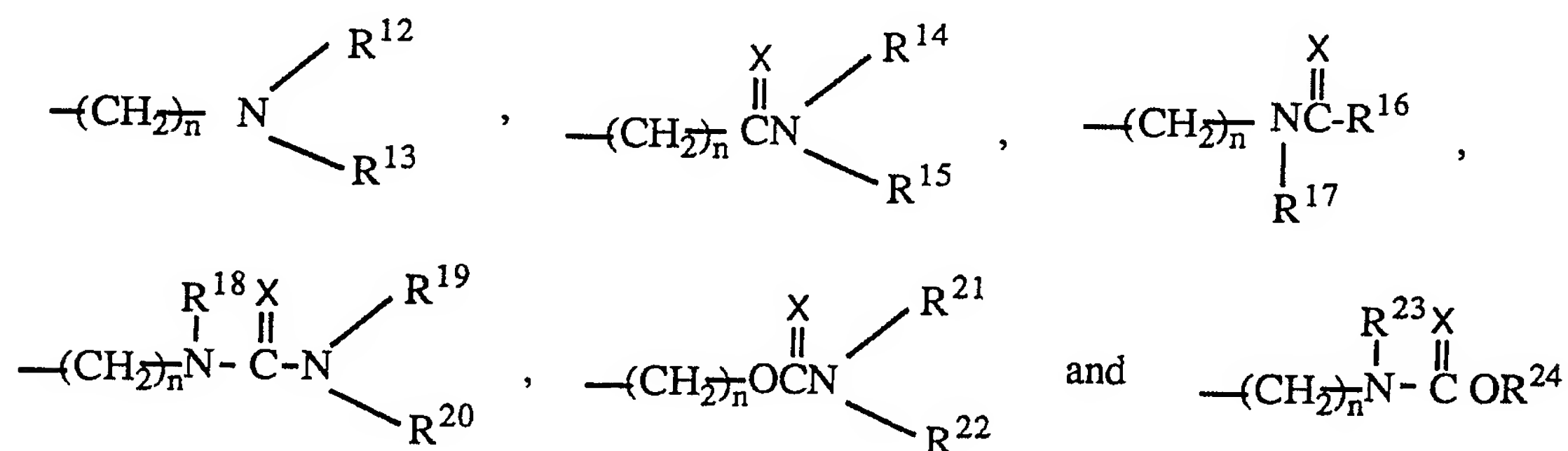
Preferred compounds of Formula I, from which a cleavable component may be selected, are all characterized in having a substituent, other than hydrido, at each of the four- and five-positions of the imidazole ring. Such substituents are selected from the aforementioned  $R^1$  and  $R^2$  groups.

The phrase "acidic group selected to contain at least one acidic hydrogen atom", as used to define the  $-Y_nA$  moiety, is intended to embrace chemical groups which, when attached to any of the  $R^3$  through  $R^{11}$  positions of Formula I, confers acidic character to the compound of Formula I. "Acidic character" means proton-donor capability, that is, the capacity of the compound of Formula I to be a proton donor in the presence of a proton-receiving substance such as water. Typically, the acidic group should be selected to have proton-donor capability such that the product compound of Formula I has a  $pK_a$  in a range from about one to about twelve. More typically, the Formula I compound would have a  $pK_a$  in a range from about two to about seven. An example of an acidic group containing at least one acidic hydrogen atom is carboxyl group ( $-COOH$ ). Where  $n$  is zero and  $A$  is  $-COOH$ , in the  $-Y_nA$  moiety, such carboxyl group would be attached directly to one of the  $R^3$  through  $R^{11}$  positions. The Formula I compound may have one

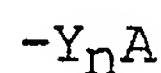
-Y<sub>n</sub>A moiety attached at one of the R<sup>3</sup> through R<sup>11</sup> positions, or may have a plurality of such -Y<sub>n</sub>A moieties attached at more than one of the R<sup>3</sup> through R<sup>11</sup> positions, up to a maximum of nine such -Y<sub>n</sub>A moieties. There are many examples of acidic groups other than carboxyl group, selectable to contain at least one acidic hydrogen atom. Such other acidic groups may be collectively referred to as "bioisosteres of carboxylic acid" or referred to as "acidic bioisosteres". Specific examples of such acidic bioisosteres are described hereinafter. Compounds of Formula I having the -Y<sub>n</sub>A moiety attached at one of positions R<sup>5</sup>, R<sup>6</sup>, R<sup>8</sup> and R<sup>9</sup> would be expected to have preferred properties, while attachment at R<sup>5</sup> or R<sup>9</sup> would be more preferred.

A preferred class of compounds within the sub-class defined by Formula I consists of those compounds wherein m is one; wherein each of R<sup>0</sup> through R<sup>11</sup> is independently selected from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, mercaptocarbonyl, mercaptothiocarbonyl, mercaptoalkyl, alkoxycarbonyloxy, alkylthio, cycloalkylthio, alkylthiocarbonyl, alkylcarbonylthio, alkylthiocarbonyloxy, alkylthiocarbonylthio, alkylthiothiocarbonyl, alkylthiothiocarbonylthio, arylthio, arylthiocarbonyl, arylcarbonylthio, arylthiocarbonyloxy, arylthiocarbonylthio, arylthiothiocarbonyl, arylthiothiocarbonylthio, aralkylthio, aralkylthiocarbonyl, aralkylcarbonylthio, aralkylthiocarbonyloxy, aralkylthiocarbonylthio, aralkylthiocarbonyl, aralkylthiocarbonylthio, mercapto,

- alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, phthalimido, phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and
- 5 cycloheteroalkylcarbonylalkyl wherein each of said heteroaryl- and cycloheteroalkyl-containing groups has one or more hetero ring atoms selected from oxygen, sulfur and nitrogen atoms, and wherein each of  $R^0$  through  $R^{11}$  may be
- 10 further independently selected from amino and amido radicals of the formula

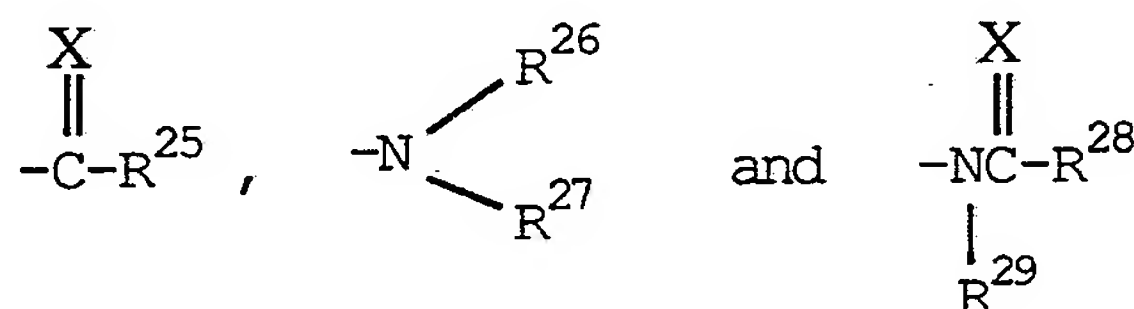


- 15 wherein X is selected from oxygen atom or sulfur atom;
- wherein each n is a number independently selected from zero to six, inclusive;
- 20 wherein each of  $R^{12}$  through  $R^{24}$  is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl;
- 25 and wherein each of  $R^3$  through  $R^{11}$  may be further independently selected from hydrido and haloalkyl, and from acidic moieties of the formula

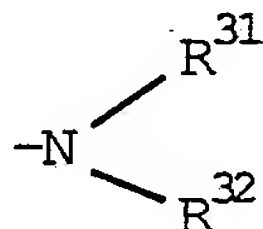


wherein n is a number selected from zero through three, inclusive; wherein A is an acidic group selected from acids containing one or more atoms selected from oxygen, sulfur, phosphorus and nitrogen atoms, and wherein said acidic group is selected to contain at least one acidic hydrogen atom, and the amide, ester and salt derivatives of said acidic moieties; wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aryl, aralkyl and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms;

and wherein any of the foregoing  $R^1$  through  $R^{24}$ , Y and A groups having a substitutable position may be substituted with one or more groups selected from alkyl, alkenyl, aralkyl, hydroxyalkyl, trifluoromethyl, difluoroalkyl, alkoxy, aryloxy, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, carboxyl, mercaptocarbonyl, alkylthio, alkylthiocarbonyl, and amino and amido radicals of the formula



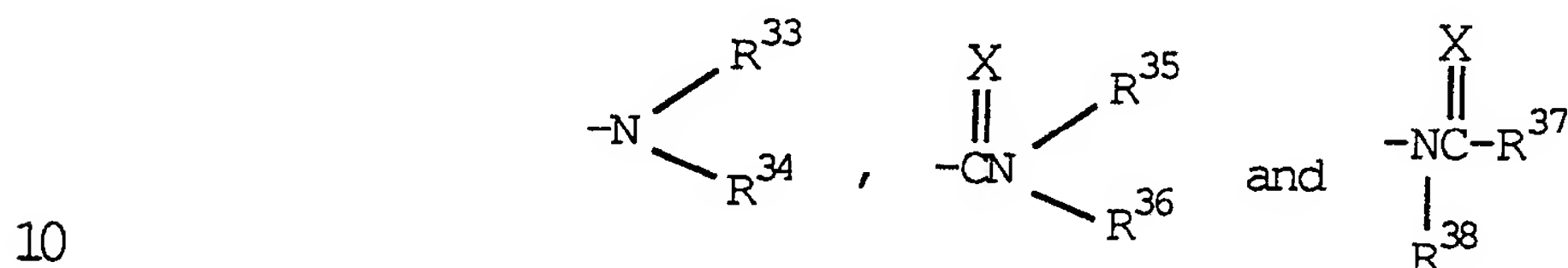
wherein X is selected from oxygen atom and sulfur atom; wherein  $R^{25}$  is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, and  $\text{DR}^{30}$  and



wherein D is selected from oxygen atom and sulfur atom, and  $R^{30}$  is selected from hydrido, alkyl, cycloalkyl,

**SUBSTITUTE SHEET**

cycloalkylalkyl, aralkyl and aryl; wherein each of R<sup>26</sup>, R<sup>27</sup>, R<sup>28</sup>, R<sup>29</sup>, R<sup>31</sup> and R<sup>32</sup> is independently selected from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, alkanoyl, alkoxycarbonyl, carboxyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl, and wherein each of R<sup>26</sup>, R<sup>27</sup>, R<sup>28</sup>, R<sup>29</sup>, R<sup>31</sup> and R<sup>32</sup> is further independently selected from amino and amido radicals of the formula



wherein X is selected from oxygen atom or sulfur atom;

15 wherein each of R<sup>26</sup> through R<sup>31</sup> is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl;

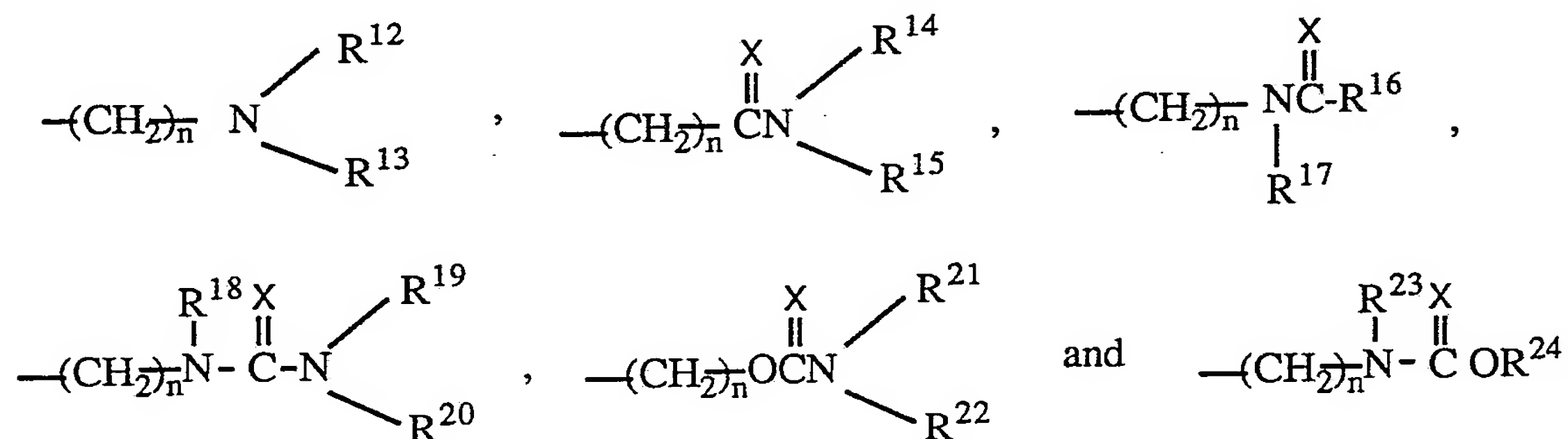
20 with the proviso that at least one of said R<sup>1</sup> through R<sup>24</sup>, Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

25 or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

30 A more preferred class of compounds within the subclass defined by Formula I consists of those compounds wherein m is one; wherein each of R<sup>0</sup> through R<sup>11</sup> is independently selected from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl,



- alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, mercaptocarbonyl, alkoxycarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl,
- 5 aralkylcarbonyloxyalkyl, alkylthio, cycloalkylthio, arylthio, aralkylthio, aralkylthiocarbonylthio, mercapto, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, phthalimido, phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and
- 10 cycloheteroalkylcarbonylalkyl wherein each of said heteroaryl- and cycloheteroalkyl-containing groups has one or more hetero ring atoms selected from oxygen, sulfur and nitrogen atoms, and wherein each of  $R^0$  through  $R^{11}$  may be further independently selected from amino and amido radicals
- 15 of the formula



- 20 wherein X is selected from oxygen atom or sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

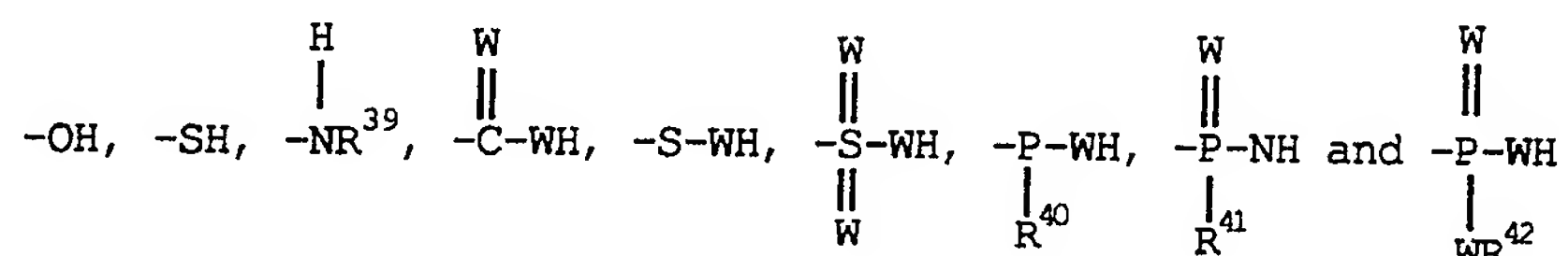
- 25 wherein each of  $R^{12}$  through  $R^{24}$  is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl;

and wherein each of  $R^3$  through  $R^{11}$  may be an acidic moiety further independently selected from hydrido and haloalkyl, and from acidic moieties of the formula

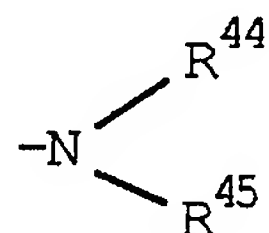


wherein  $n$  is a number selected from zero through three, inclusive;

10 wherein  $A$  is selected from carboxylic acid and bioisosteres of carboxylic acid selected from



15 wherein each  $W$  is independently selected from oxygen atom, sulfur atom and  $NR^{43}$ ; wherein each of  $R^{39}$ ,  $R^{40}$ ,  $R^{41}$ ,  $R^{42}$  and  $R^{43}$  is independently selected from hydrido, alkyl, haloalkyl, haloalkylsulfonyl, haloalkylcarbonyl, cycloalkyl, cycloalkylalkyl, aryl and aralkyl; wherein each of  $R^{39}$ ,  $R^{40}$ ,  $R^{41}$  and  $R^{42}$  may be further independently selected from amino radicals of the formula



25 wherein each of  $R^{44}$  and  $R^{45}$  is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl, and wherein  $R^{44}$  and  $R^{45}$  taken together may form a heterocyclic group having five to seven ring members including the nitrogen atom

30 of said amino radical, which heterocyclic group may further

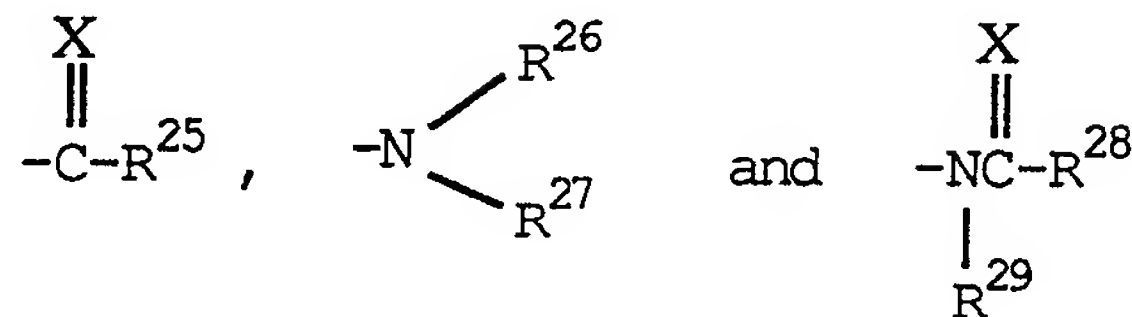
contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms and which heterocyclic group may be saturated or partially unsaturated; wherein R<sup>44</sup> and R<sup>45</sup> taken together may form an aromatic heterocyclic group having  
5 five ring members including the nitrogen atom of said amino radical and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms; wherein each of R<sup>40</sup> and R<sup>41</sup> may be further independently selected from hydroxy, alkoxy,  
10 alkylthio, aryloxy, arylthio, aralkylthio and aralkoxy; and the amide, ester and salt derivatives of said acidic groups;

wherein said bioisostere of carboxylic acid may be further selected from heterocyclic acidic groups consisting of  
15 heterocyclic rings of four to about nine ring members, which heterocyclic ring contains at least one hetero atom selected from oxygen, sulfur and nitrogen atoms, which heterocyclic ring may be saturated, fully unsaturated or partially unsaturated, and which heterocyclic ring may be attached at a  
20 single position selected from R<sup>3</sup> through R<sup>11</sup> or may be attached at any two adjacent positions selected from R<sup>3</sup> through R<sup>11</sup> so as to form a fused-ring system with one of the phenyl rings of the biphenyl moiety of Formula I; and the amide, ester and salt derivatives of said heterocyclic acidic  
25 groups;

wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, aryl and aralkyl;

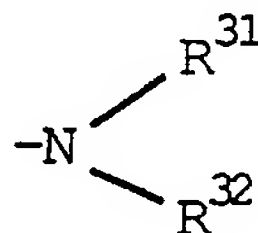
30 and wherein any of the foregoing R<sup>1</sup> through R<sup>24</sup>, Y and A groups having a substitutable position may be substituted by one or more groups selected from alkyl, difluoroalkyl, alkenyl, aralkyl, hydroxyalkyl, trifluoromethyl, alkoxy,  
35 aryloxy, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl,

carboxyl, mercaptocarbonyl, alkylthio, alkylthiocarbonyl, and amino and amido radicals of the formula



5

wherein X is selected from oxygen atom and sulfur atom;  
wherein R<sup>25</sup> is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl and DR<sup>30</sup> and



10

wherein D is selected from oxygen atom and sulfur atom,  
wherein R<sup>30</sup> is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl and aryl;

15

wherein each of R<sup>26</sup>, R<sup>27</sup>, R<sup>28</sup>, R<sup>29</sup>, R<sup>31</sup> and R<sup>32</sup> is  
independently selected from hydrido, alkyl, cycloalkyl, cyano,  
hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl,  
alkanoyl, alkoxycarbonyl, carboxyl, haloalkylsulfinyl,  
haloalkylsulfonyl, aralkyl and aryl;

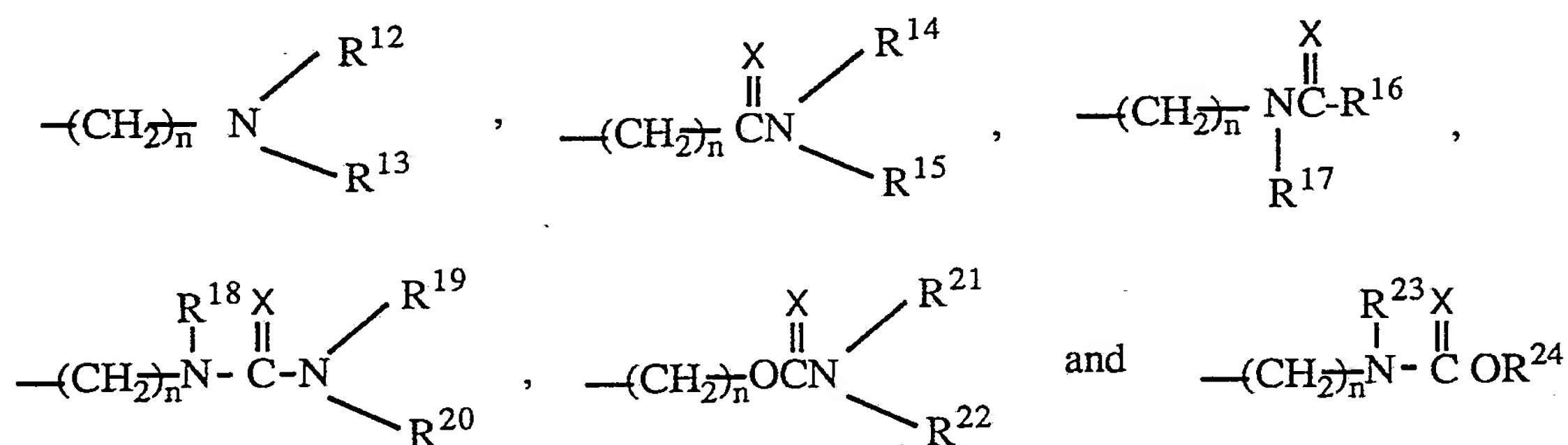
20

with the proviso that at least one of said R<sup>1</sup> through R<sup>24</sup>, Y  
and A substituents contains a terminal primary or secondary  
amino moiety or a moiety convertible to a primary or secondary  
amino moiety;

25

or a tautomer thereof or a pharmaceutically-acceptable salt  
thereof.

An even more preferred class of compounds within the sub-class defined by Formula I consists of those compounds wherein m is one; wherein each of R<sup>0</sup>, R<sup>1</sup> and R<sup>2</sup> is independently selected from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, mercaptocarbonyl, mercaptoalkyl, alkoxycarbonyloxy, alkylthio, cycloalkylthio, arylthio, aralkylthio, mercapto, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, phthalimido, phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and cycloheteroalkylcarbonylalkyl wherein each of said heteroaryl- and cycloheteroalkyl-containing groups has one or more hetero ring atoms selected from oxygen, sulfur and nitrogen atoms, and wherein each of R<sup>0</sup> through R<sup>11</sup> may be further independently selected from amino and amido radicals of the formula



wherein X is selected from oxygen atom and sulfur atom;



wherein each n is a number independently selected from zero to six, inclusive;

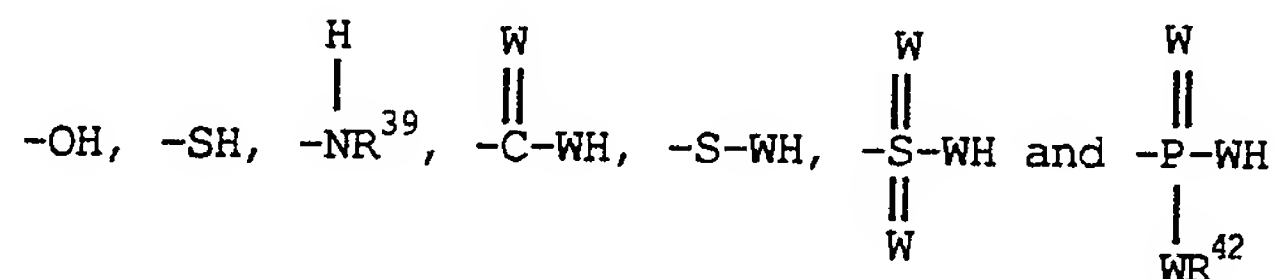
5 wherein each of R<sup>12</sup> through R<sup>24</sup> is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl;

10 wherein each of R<sup>3</sup> through R<sup>11</sup> is independently selected from hydrido, hydroxy, alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, cyano, nitro, carboxyl, alkylthio, aralkylthio, mercapto, alkylsulfinyl, 15 alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms;

20 and wherein each of R<sup>3</sup> through R<sup>11</sup> may be an acidic moiety further independently selected from acidic moieties of the formula

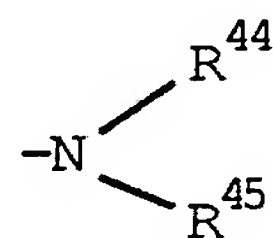


25 wherein n is a number selected from zero through three, inclusive; wherein A is selected from carboxylic acid and bioisosteres of carboxylic acid selected from



30 wherein each W is independently selected from oxygen atom, sulfur atom and NR<sup>43</sup>; wherein each of R<sup>39</sup>, R<sup>42</sup> and R<sup>43</sup> is independently selected from hydrido, alkyl, haloalkyl, haloalkylsulfonyl, haloalkylcarbonyl, cycloalkyl,

cycloalkylalkyl, aryl and aralkyl; wherein each of R<sup>39</sup> and R<sup>42</sup> may be further independently selected from amino radical of the formula



5

wherein each of R<sup>44</sup> and R<sup>45</sup> is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl, and wherein R<sup>44</sup> and R<sup>45</sup> taken together may form a heterocyclic group having five to seven ring members including the nitrogen atom of said amino radical, which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms, and which heterocyclic group may be saturated or partially unsaturated; wherein R<sup>44</sup> and R<sup>45</sup> taken together may form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino radical and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms; and the amide, ester and salt derivatives of said acidic groups; wherein said bioisostere of carboxylic acid may be further selected from heterocyclic acidic groups consisting of heterocyclic rings of four to about nine ring members, which ring contains at least one hetero atom, selected from oxygen, sulfur and nitrogen atoms, which heterocyclic ring may be saturated, fully unsaturated or partially unsaturated, and which heterocyclic ring may be attached at a single position selected from R<sup>3</sup> through R<sup>11</sup> or may be attached at any two adjacent positions selected from R<sup>3</sup> through R<sup>11</sup> so as to form a fused-ring system with one of the phenyl rings of Formula I; and the amide, ester and salt derivatives of said heterocyclic acidic groups;

wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, aryl and aralkyl;

5

wherein each of R<sup>1</sup> through R<sup>24</sup>, Y and A independently may be substituted at any substitutable position with one or more groups selected from alkyl, cycloalkyl, cycloalkylalkyl, hydroxy, oxo, trifluoromethyl, difluoroalkyl, alkoxycarbonyl, cyano, nitro, alkylsulfonyl, haloalkylsulfonyl, aryl, aralkyl, alkoxy, aryloxy and aralkoxy;

10

with the proviso that at least one of said R<sup>1</sup> through R<sup>24</sup>, Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

15

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

20

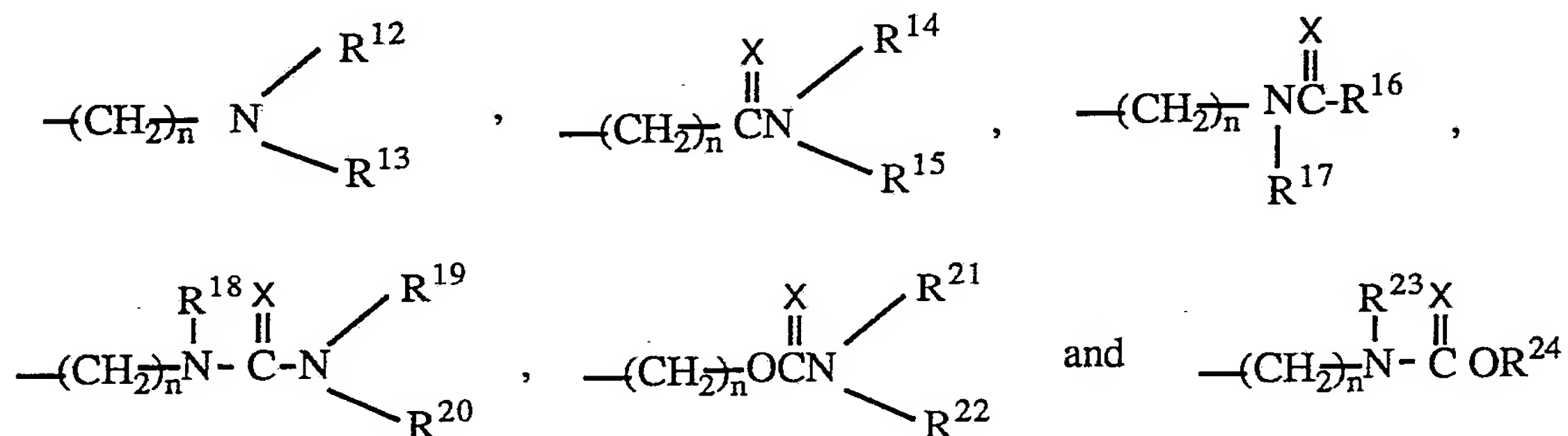
A highly preferred class of compounds within the sub-class defined by Formula I consists of those compounds wherein m is one; wherein each of R<sup>0</sup>, R<sup>1</sup> and R<sup>2</sup> is independently selected from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, benzoyl, phenoxy, phenoxyalkyl, phenalkyloxy, phenylthio, phenalkylthio, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, mercaptocarbonyl, mercaptoalkyl, alkoxycarbonyloxy, alkylthio, cycloalkylthio, phthalimido, phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and cycloheteroalkylcarbonylalkyl wherein each of said heteroaryl-

25

30

35

and cycloheteroalkyl-containing groups has one or more hetero ring atoms selected from oxygen, sulfur and nitrogen atoms, and wherein each of  $R^0$  through  $R^{11}$  may be further independently selected from amino and amido radicals of the  
 5 formula



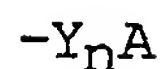
10 wherein X is selected from oxygen atom and sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

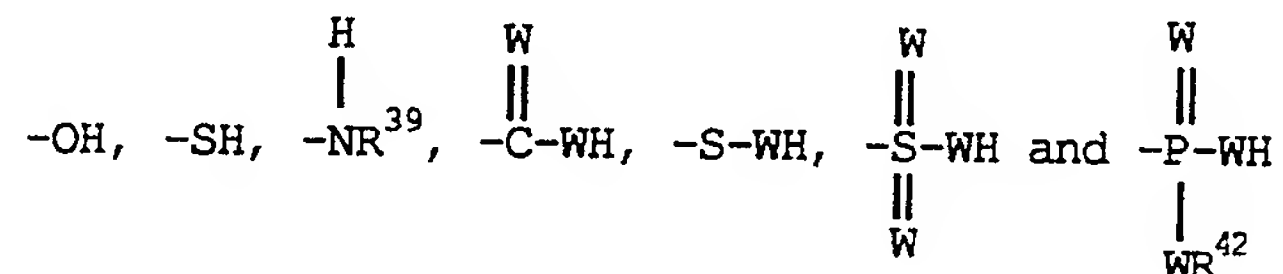
15 wherein each of  $R^{12}$  through  $R^{24}$  is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, hydroxyalkyl, alkoxyalkyl, phenalkyl and phenyl;

wherein each of  $R^3$  through  $R^{11}$  is independently selected from  
 20 hydrido, hydroxy, alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, phenalkyl, phenyl, benzoyl, phenoxy, phenalkyloxy, alkoxyalkyl, alkylcarbonyl, alkoxy carbonyl, alkenyl, cyano, nitro, carboxyl, alkylthio, mercapto and heteroaryl having one or more ring atoms selected  
 25 from oxygen, sulfur and nitrogen atoms;

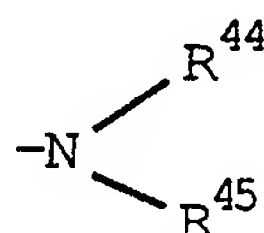
and wherein each of  $R^3$  through  $R^{11}$  may be an acidic moiety further independently selected from acidic moieties of the formula



wherein n is a number selected from zero through two, inclusive; wherein A is selected from carboxylic acid and  
 5 bioisosteres of carboxylic acid selected from



wherein each W is independently selected from oxygen atom,  
 10 sulfur atom and  $NR^{43}$ ; wherein each of  $R^{39}$ ,  $R^{42}$  and  $R^{43}$  is independently selected from hydrido, alkyl, haloalkyl, haloalkylsulfonyl, haloalkylcarbonyl, cycloalkyl, phenyl and benzyl; wherein each of  $R^{39}$  and  $R^{42}$  may be further  
 15 independently selected from amino radical of the formula



wherein each of  $R^{44}$  and  $R^{45}$  is independently selected from  
 20 hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, alkoxyalkyl, benzyl and phenyl; and the amide, ester and salt derivatives of said acidic groups;

wherein said bioisostere of carboxylic acid may be further  
 25 selected from heterocyclic acidic groups consisting of heterocyclic rings of four to about nine ring members, which ring contains at least one hetero atom, selected from oxygen, sulfur and nitrogen atoms, which heterocyclic ring may be saturated, fully unsaturated or partially unsaturated, and  
 30 which heterocyclic ring may be attached at a single position selected from  $R^3$  through  $R^{11}$  or may be attached at any two adjacent positions selected from  $R^3$  through  $R^{11}$  so as to form

a fused-ring system with one of the phenyl rings of the biphenyl moiety of Formula I; and the amide, ester and salt derivatives of said heterocyclic acidic groups;

5 wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, phenyl, phenalkyl and aralkyl;

10 wherein each of R<sup>1</sup> through R<sup>24</sup>, Y and A and independently may be substituted at any substitutable position with one or more groups selected from alkyl, cycloalkyl, cycloalkylalkyl, hydroxy, oxo, trifluoromethyl, difluoroalkyl, alkoxy carbonyl, cyano, nitro, alkylsulfonyl, haloalkylsulfonyl, aryl, aralkyl, alkoxy, aryloxy and aralkoxy;

15 with the proviso that at least one of said R<sup>1</sup> through R<sup>24</sup>, Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

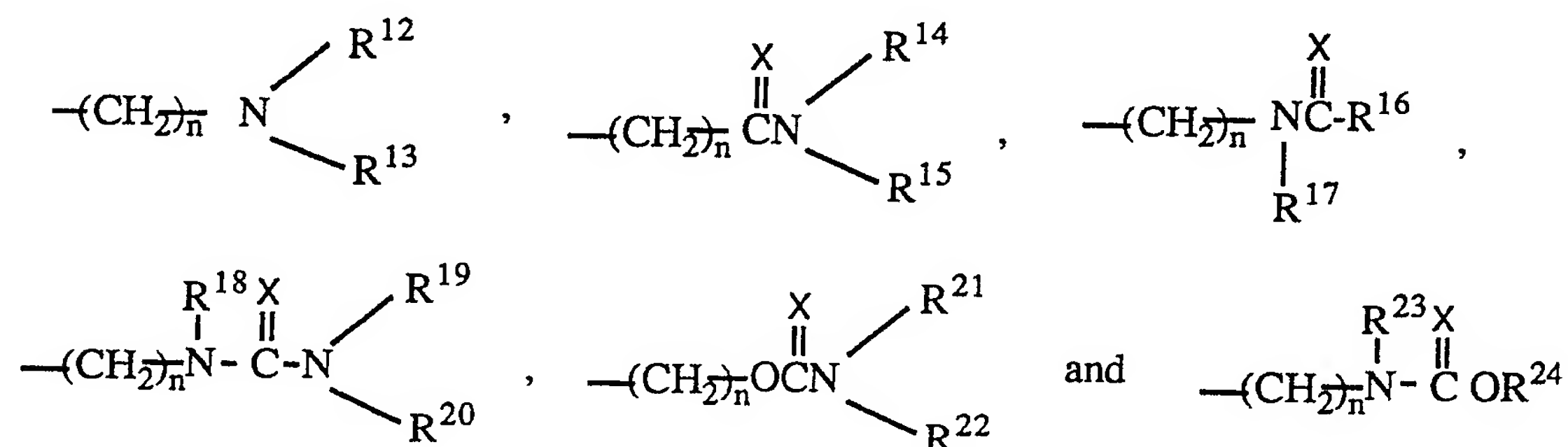
20 or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

An even more highly preferred class of compounds  
25 within Formula I consists of those compounds wherein m is one; wherein R<sup>0</sup> is selected from alkyl, alkenyl, phenyl, alkylthio, cycloalkyl, cycloalkylalkyl and cycloalkylthio; wherein each of R<sup>1</sup> and R<sup>2</sup> is independently selected from alkyl, aminoalkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl,  
30 alkoxy, aralkyl, aryl, benzoyl, phenoxy, phenoxyalkyl, phenalkyloxy, phenylthio, phenalkylthio, aralkoxy, alkoxyalkyl, acetyl, alkoxy carbonyl, alkenyl, cycloalkenyl, alkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, mercaptoalkyl, mercapto carbonyl,  
35 alkoxy carbonyloxy, alkylcarbonyloxyalkyl, alkoxy carbonylalkyl,



aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, phthalimido, phthalimidoalkyl, imidazoalkyl, tetrazole, tetrazolealkyl, alkylthio, cycloalkylthio, and amino and amido radicals of the formula

5



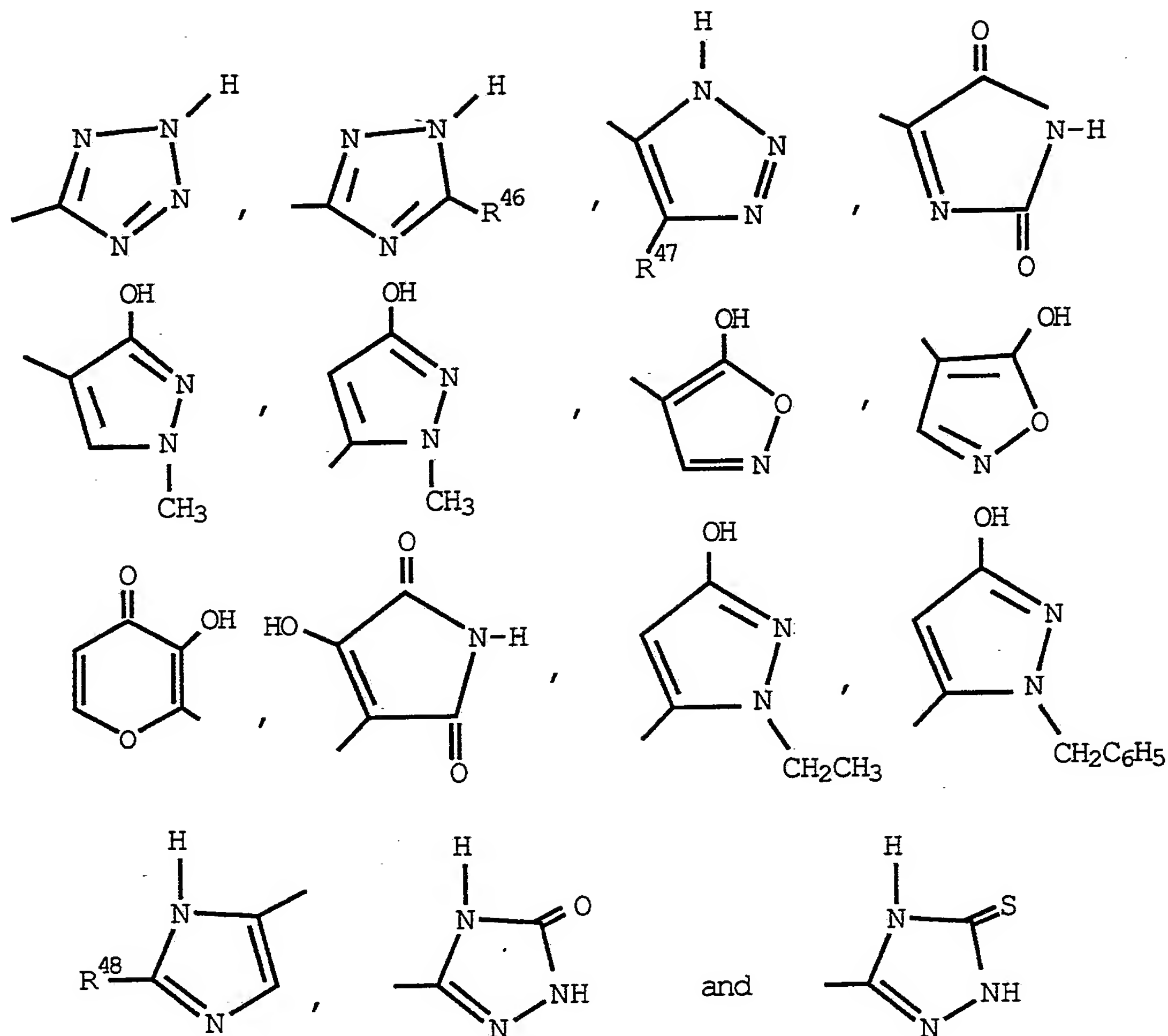
wherein X is selected from oxygen atom and sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

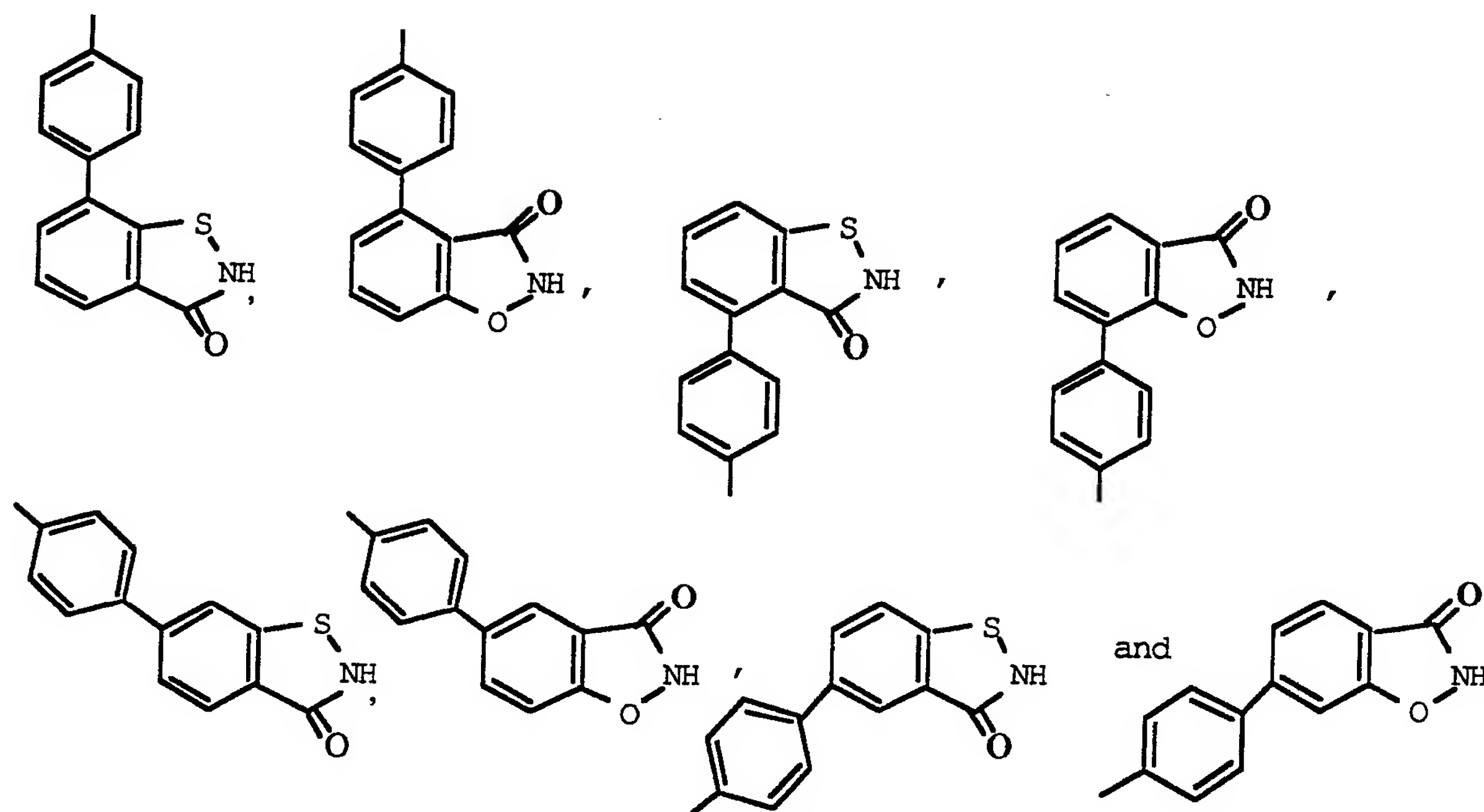
15 wherein each of R<sup>12</sup> through R<sup>24</sup> is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, hydroxyalkyl, alkoxyalkyl, phenalkyl and phenyl;

wherein each of R<sup>3</sup> through R<sup>11</sup> is independently selected from hydrido, hydroxy, alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, phenalkyl, phenyl, benzoyl, phenoxy, phenalkyloxy, alkoxyalkyl, acetyl, alkoxycarbonyl, alkenyl, cyano, nitro, carboxyl, alkylthio and mercapto;

25 and wherein each of R<sup>3</sup> through R<sup>11</sup> may be an acidic moiety further independently selected from acidic moieties consisting of CO<sub>2</sub>H, CO<sub>2</sub>CH<sub>3</sub>, SH, CH<sub>2</sub>SH, C<sub>2</sub>H<sub>4</sub>SH, PO<sub>3</sub>H<sub>2</sub>, NHSO<sub>2</sub>CF<sub>3</sub>, NHSO<sub>2</sub>C<sub>6</sub>F<sub>5</sub>, SO<sub>3</sub>H, CONHNH<sub>2</sub>, CONHNHSO<sub>2</sub>CF<sub>3</sub>, CONHOCH<sub>3</sub>, CONHOC<sub>2</sub>H<sub>5</sub>, CONHCF<sub>3</sub>, OH, CH<sub>2</sub>OH, C<sub>2</sub>H<sub>4</sub>OH, OPO<sub>3</sub>H<sub>2</sub>, OSO<sub>3</sub>H,





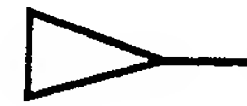
wherein each of  $R^{46}$ ,  $R^{47}$  and  $R^{48}$  is independently selected  
 5 from H, Cl, CN,  $\text{NO}_2$ ,  $\text{CF}_3$ ,  $\text{C}_2\text{F}_5$ ,  $\text{C}_3\text{F}_7$ ,  $\text{CHF}_2$ ,  $\text{CH}_2\text{F}$ ,  $\text{CO}_2\text{CH}_3$ ,  
 $\text{CO}_2\text{C}_2\text{H}_5$ ,  $\text{SO}_2\text{CH}_3$ ,  $\text{SO}_2\text{CF}_3$  and  $\text{SO}_2\text{C}_6\text{F}_5$ ; wherein Z is selected  
 from O, S,  $\text{NR}^{49}$  and  $\text{CH}_2$ ; wherein  $R^{49}$  is selected from hydrido,  
 $\text{CH}_3$  and  $\text{CH}_2\text{C}_6\text{H}_5$ ; and wherein said acidic moiety may be a  
 heterocyclic acidic group attached at any two adjacent  
 10 positions of  $R^3$  through  $R^{11}$  so as to form a fused ring system  
 so as to include one of the phenyl rings of the biphenyl  
 moiety of Formula I, said biphenyl fused ring system selected  
 from



and the esters, amides and salts of said acidic moieties;

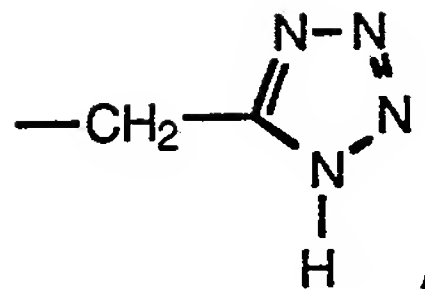
- 5 with the proviso that at least one of said  $R^1$  through  $R^{24}$  substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;
- 10 or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

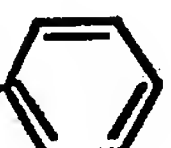
A class of compounds of particular interest within Formula I consists of those compounds wherein  $m$  is one;

15 wherein  $R^0$  is selected from  $C_4H_9(n)$ ,  $CH_3CH_2CH=CH$ ,  $C_3H_7(n)$ ,  $SC_3H_7$ ,   $CH_2$ , ,  $C_2H_5$ ,  $C_5H_{11}(n)$ ,  $C_6H_{13}(n)$ ,  $SC_4H_9$ ,   $CH_2S$ ,  $CH_3CH=CH$  and  $CH_3CH_2CH_2CH=CH-$ ; wherein each of  $R^1$  and  $R^2$  is independently selected from amino, aminomethyl, aminoethyl, aminopropyl,  $CH_2OH$ ,  $CH_2OCOCH_3$ ,  $CH_2Cl$ ,  $Cl$ ,  $CH_2OCH_3$ ,  $CH_2OCH(CH_3)_2$ ,  $I$ ,  $CHO$ ,

20

CH<sub>2</sub>CO<sub>2</sub>H, CH(CH<sub>3</sub>)CO<sub>2</sub>H, NO<sub>2</sub>, Cl,



-CH<sub>2</sub>OCOCH<sub>2</sub>CH<sub>2</sub>-, -CO<sub>2</sub>CH<sub>3</sub>, -CONH<sub>2</sub>, -CONHCH<sub>3</sub>, CON(CH<sub>3</sub>)<sub>2</sub>,

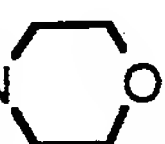
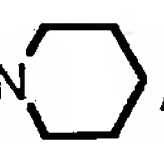
-CH<sub>2</sub>-NHCO<sub>2</sub>C<sub>2</sub>H<sub>5</sub>, -CH<sub>2</sub>NHCO<sub>2</sub>-, -CH<sub>2</sub>NHCO<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>NHCO<sub>2</sub>C<sub>3</sub>H<sub>7</sub>,

-CH<sub>2</sub>NHCO<sub>2</sub>CH<sub>2</sub>(CH<sub>3</sub>)<sub>2</sub>, -CH<sub>2</sub>NHCO<sub>2</sub>C<sub>4</sub>H<sub>9</sub>, CH<sub>2</sub>NHCO<sub>2</sub>-adamantyl,

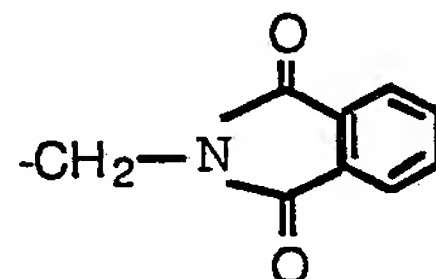
5 -CH<sub>2</sub>NHCO<sub>2</sub>-(1-naphthyl), -CH<sub>2</sub>NHCONHCH<sub>3</sub>, -CH<sub>2</sub>NHCONHC<sub>2</sub>H<sub>5</sub>,

-CH<sub>2</sub>NHCONHC<sub>3</sub>H<sub>7</sub>, -CH<sub>2</sub>NHCONHC<sub>4</sub>H<sub>9</sub>, -CH<sub>2</sub>NHCONHCH(CH<sub>3</sub>)<sub>2</sub>,

-CH<sub>2</sub>NHCONH(1-naphthyl), -CH<sub>2</sub>NHCONH(1-adamantyl), CO<sub>2</sub>H,

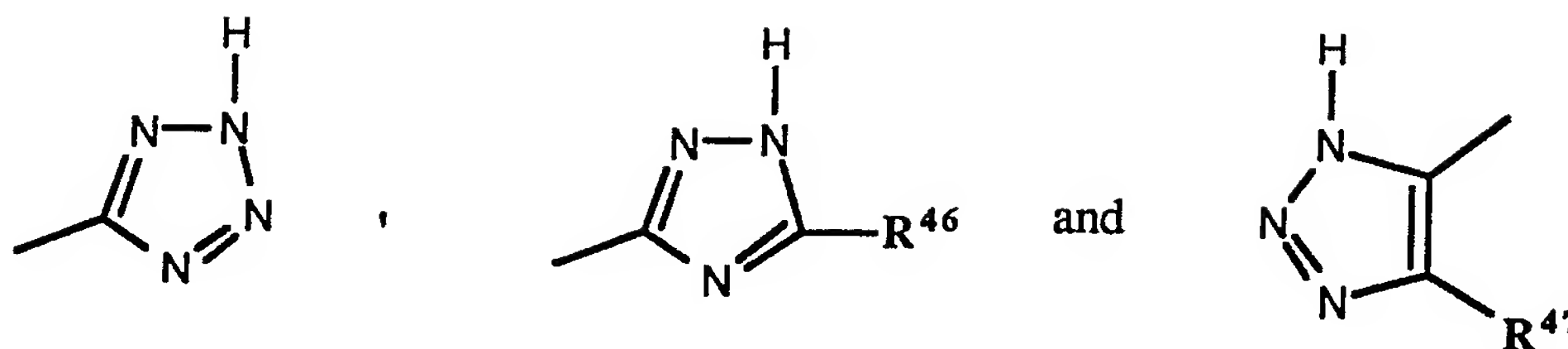
-CH<sub>2</sub>CH<sub>2</sub>-CO-N, -CH<sub>2</sub>CH<sub>2</sub>CO-N, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CO<sub>2</sub>H,

-CH<sub>2</sub>CH<sub>2</sub>F, -CH<sub>2</sub>OCONHCH<sub>3</sub>, -CH<sub>2</sub>OCSNHCH<sub>3</sub>, -CH<sub>2</sub>NHCSOC<sub>3</sub>H<sub>7</sub>,



10 -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>F, -CH<sub>2</sub>ONO<sub>2</sub>,

H, Cl, NO<sub>2</sub>, CF<sub>3</sub>, CH<sub>2</sub>OH, Br, F, I, methyl, ethyl, n-propyl,  
isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl,  
isopentyl, neopentyl, phenyl, benzyl, phenethyl, cyclohexyl,  
cyclohexylmethyl, 1-oxoethyl, 1-oxopropyl, 1-oxobutyl, 1-  
15 oxopentyl, 1,1-dimethoxypropyl, 1,1-dimethoxybutyl, 1,1-  
dimethoxypentyl, hydroxyalkyl, halo, difluoromethyl, 1,1-  
difluoroethyl, 1,1-difluoropropyl, 1,1-difluorobutyl and 1,1-  
difluoropentyl; wherein each of R<sup>3</sup> through R<sup>11</sup> is hydrido, with  
the proviso that at least one of R<sup>5</sup>, R<sup>6</sup>, R<sup>8</sup> and R<sup>9</sup> is an  
20 acidic group selected from CO<sub>2</sub>H, SH, PO<sub>3</sub>H<sub>2</sub>, SO<sub>3</sub>H, CONHNH<sub>2</sub>,  
CONHNHSO<sub>2</sub>CF<sub>3</sub>, OH,



wherein each of R<sup>46</sup> and R<sup>47</sup> is independently selected from Cl, CN, NO<sub>2</sub>, CF<sub>3</sub>, CO<sub>2</sub>CH<sub>3</sub> and SO<sub>2</sub>CF<sub>3</sub>;

5


with the proviso that at least one of said R<sup>1</sup> through R<sup>11</sup> substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

10


or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

A class of compounds of more particular interest within Formula I consists of those compounds wherein m is one; wherein R<sup>0</sup> is selected from C<sub>4</sub>H<sub>9</sub>(n), CH<sub>3</sub>CH<sub>2</sub>CH=CH, C<sub>3</sub>H<sub>7</sub>(n),

SC<sub>3</sub>H<sub>7</sub>, , , C<sub>2</sub>H<sub>5</sub>, C<sub>5</sub>H<sub>11</sub>(n), C<sub>6</sub>H<sub>13</sub>(n),

SC<sub>4</sub>H<sub>9</sub>, , CH<sub>3</sub>CH=CH and CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>CH=CH-; wherein R<sup>1</sup>

is selected from amino, aminomethyl, aminoethyl, aminopropyl, CH<sub>2</sub>OH, CH<sub>2</sub>OCOCH<sub>3</sub>, CH<sub>2</sub>Cl, Cl, CH<sub>2</sub>OCH<sub>3</sub>, CH<sub>2</sub>OCH(CH<sub>3</sub>)<sub>2</sub>, I, CHO, CH<sub>2</sub>CO<sub>2</sub>H, CH(CH<sub>3</sub>)CO<sub>2</sub>H, -CO<sub>2</sub>CH<sub>3</sub>, -CONH<sub>2</sub>, -CONHCH<sub>3</sub>, CON(CH<sub>3</sub>)<sub>2</sub>, -

CH<sub>2</sub>-NHCO<sub>2</sub>C<sub>2</sub>H<sub>5</sub>, -CH<sub>2</sub>NHCO<sub>2</sub>-, -CH<sub>2</sub>NHCO<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>NHCO<sub>2</sub>C<sub>3</sub>H<sub>7</sub>, -

CH<sub>2</sub>NHCO<sub>2</sub>CH<sub>2</sub>(CH<sub>3</sub>)<sub>2</sub>, -CH<sub>2</sub>NHCO<sub>2</sub>C<sub>4</sub>H<sub>9</sub>, CH<sub>2</sub>NHCO<sub>2</sub>-adamantyl, -

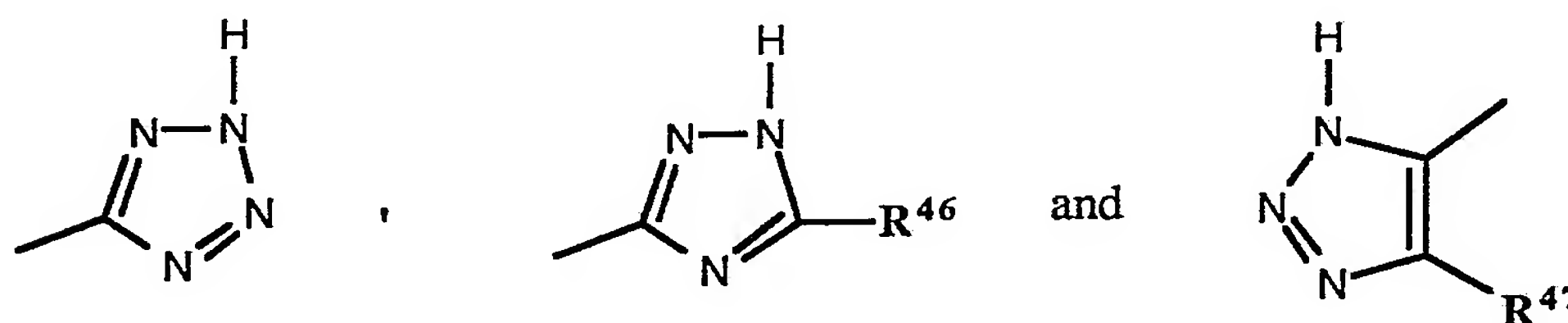
CH<sub>2</sub>NHCO<sub>2</sub>-(1-naphthyl), -CH<sub>2</sub>NHCONHCH<sub>3</sub>, -CH<sub>2</sub>NHCONHC<sub>2</sub>H<sub>5</sub>, -

CH<sub>2</sub>NHCONHC<sub>3</sub>H<sub>7</sub>, -CH<sub>2</sub>NHCONHC<sub>4</sub>H<sub>9</sub>, -CH<sub>2</sub>NHCONHCH(CH<sub>3</sub>)<sub>2</sub>, -

CH<sub>2</sub>NHCONH(1-naphthyl), -CH<sub>2</sub>NHCONH(1-adamantyl), CO<sub>2</sub>H,

-CH<sub>2</sub>CH<sub>2</sub>-CO-N, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CO<sub>2</sub>H,

$-\text{CH}_2\text{CH}_2\text{F}$ ,  $-\text{CH}_2\text{OCONHCH}_3$ ,  $-\text{CH}_2\text{CH}_2\text{CH}_2\text{F}$ ,  $-\text{CH}_2\text{SH}$  and  $-\text{CH}_2\text{O}-\text{C}_6\text{H}_5$ ;  
 wherein  $\text{R}^2$  is selected from H, Cl,  $\text{NO}_2$ ,  $\text{CF}_3$ ,  $\text{CH}_2\text{OH}$ , Br, F, I,  
 methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl,  
 isobutyl, tert-butyl, n-pentyl, isopentyl, neopentyl, phenyl,  
 5 benzyl, phenethyl, cyclohexyl, cyclohexylmethyl, 1-oxoethyl,  
 1-oxopropyl, 1-oxobutyl, 1-oxopentyl, 1,1-dimethoxypropyl,  
 1,1-dimethoxybutyl, 1,1-dimethoxypentyl, hydroxyalkyl, halo,  
 difluoromethyl, 1,1-difluoroethyl, 1,1-difluoropropyl, 1,1-  
 difluorobutyl and 1,1-difluoropentyl; wherein each of  $\text{R}^3$   
 10 through  $\text{R}^{11}$  is hydrido, with the proviso that at least one of  
 $\text{R}^5$ ,  $\text{R}^6$ ,  $\text{R}^8$  and  $\text{R}^9$  is an acidic group selected from  $\text{CO}_2\text{H}$ , SH,  
 $\text{PO}_3\text{H}_2$ ,  $\text{SO}_3\text{H}$ ,  $\text{CONHNH}_2$ ,  $\text{CONHNHSO}_2\text{CF}_3$ , OH,





15 wherein each of  $\text{R}^{46}$  and  $\text{R}^{47}$  is independently selected from Cl,  
 CN,  $\text{NO}_2$ ,  $\text{CF}_3$ ,  $\text{CO}_2\text{CH}_3$  and  $\text{SO}_2\text{CF}_3$ ;


20 with the proviso that at least one of said  $\text{R}^1$  through  $\text{R}^{11}$   
 substituents contains a terminal primary or secondary amino  
 moiety or a moiety convertible to a primary or secondary amino  
 moiety;

25 or a tautomer thereof or a pharmaceutically-acceptable salt  
 thereof.

A class of compounds of even more particular  
 interest within Formula I consists of those compounds wherein  
 m is one; wherein  $\text{R}^0$  is selected from  $\text{C}_4\text{H}_9(\text{n})$ ,  $\text{CH}_3\text{CH}_2\text{CH}=\text{CH}$ ,

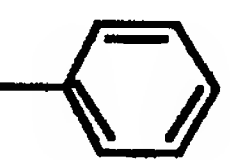


$C_3H_7(N)$ ,  $SC_3H_7$ , , ,  $C_2H_5$ ,  $C_5H_{11}(n)$ ,

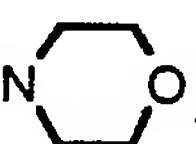
$C_6H_{13}(n)$ ,  $SC_4H_9$ , - $CH_2S$ ,  $CH_3CH=CH$  and  $CH_3CH_2CH_2CH=CH-$ ;


wherein  $R^1$  is selected from H, Cl,  $NO_2$ ,  $CF_3$ ,  $CH_2OH$ , Br, F, I, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl,

5 isobutyl, tert-butyl, n-pentyl, isopentyl, neopentyl, phenyl, benzyl, phenethyl, cyclohexyl, cyclohexylmethyl, 1-oxoethyl, 1-oxopropyl, 1-oxobutyl, 1-oxopentyl, 1,1-dimethoxypropyl, 1,1-dimethoxybutyl, 1,1-dimethoxypentyl, hydroxyalkyl, halo, difluoromethyl, 1,1-difluoroethyl, 1,1-difluoropropyl, 1,1-  
10 difluorobutyl and 1,1-difluoropentyl; wherein  $R^2$  is selected from amino, aminomethyl, aminoethyl, aminopropyl,  $CH_2OH$ ,  $CH_2OCOCH_3$ ,  $CH_2Cl$ , Cl,  $CH_2OCH_3$ ,  $CH_2OCH(CH_3)_2$ , I, CHO,  $CH_2CO_2H$ ,  $CH(CH_3)CO_2H$ , ,  $-CO_2CH_3$ ,  $-CONH_2$ ,  $-CONHCH_3$ ,  $CON(CH_3)_2$ ,

$-CH_2-NHCO_2C_2H_5$ ,  $-CH_2NHCO_2$ -,  $-CH_2NHCO_2CH_3$ ,  $-CH_2NHCO_2C_3H_7$ ,

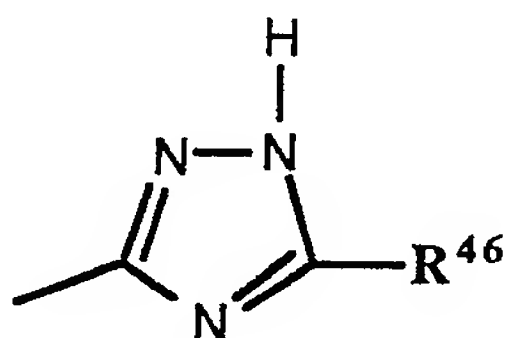
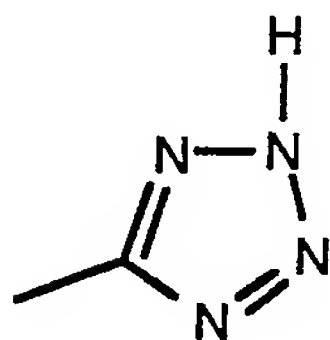
15  $-CH_2NHCO_2CH_2(CH_3)_2$ ,  $-CH_2NHCO_2C_4H_9$ ,  $CH_2NHCO_2$ -adamantyl,  $-CH_2NHCO_2$ -(1-naphthyl),  $-CH_2NHCONHCH_3$ ,  $-CH_2NHCONHC_2H_5$ ,  $-CH_2NHCONHC_3H_7$ ,  $-CH_2NHCONHC_4H_9$ ,  $-CH_2NHCONHCH(CH_3)_2$ ,  $-CH_2NHCONH$ (1-naphthyl),  $-CH_2NHCONH$ (1-adamantyl),  $CO_2H$ ,

$-CH_2CH_2-CO-N$ ,  $-CH_2CH_2CH_2CO_2H$ ,  $-CH_2CH_2F$ ,  $-CH_2OCONHCH_3$ , -

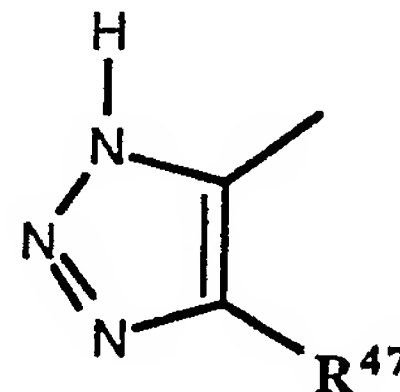
20  $CH_2CH_2CH_2F$ ,  $-CH_2SH$  and  $-CH_2O$ -;

wherein each of  $R^3$  through  $11$  is hydrido, with the proviso that at least one of  $R^5$ ,  $R^6$ ,  $R^8$  and  $R^9$  is an acidic group selected from  $CO_2H$ , SH,  $PO_3H_2$ ,  $SO_3H$ ,  $CONHNH_2$ ,  $CONHNHSO_2CF_3$ , OH,

25



and

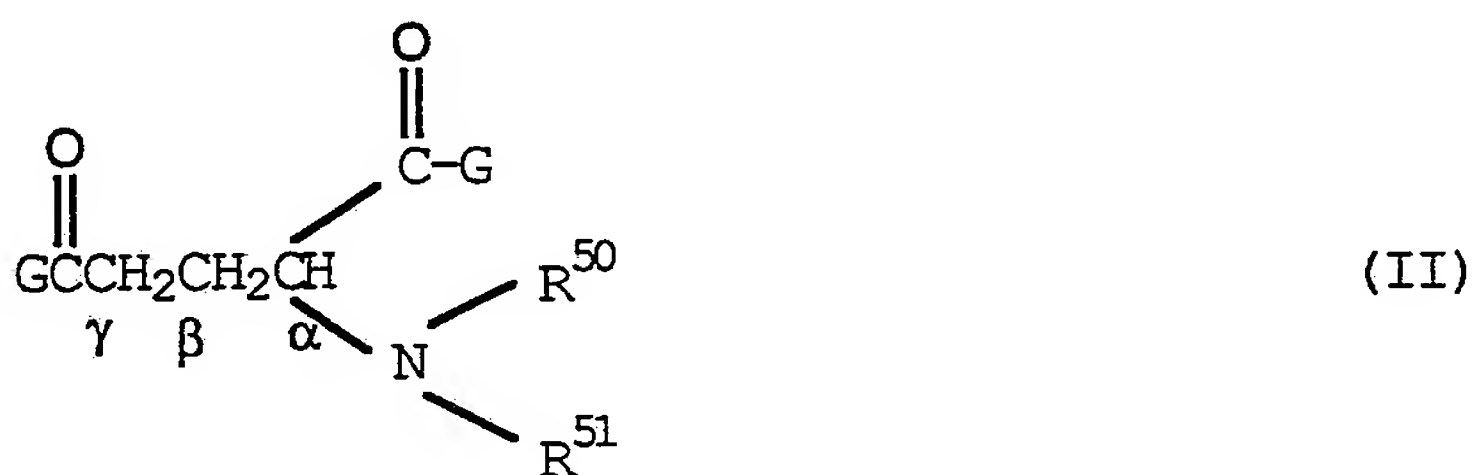


wherein each of  $R^{46}$  and  $R^{47}$  is independently selected from Cl, CN,  $NO_2$ ,  $CF_3$ ,  $CO_2CH_3$  and  $SO_2CF_3$ ;

5 with the proviso that at least one of said  $R^1$  through  $R^{11}$  substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

10 or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

The second component of a conjugate of the invention is provided by a residue which forms a kidney-enzyme-cleavable amide bond with the residue of the first-  
15 component AII antagonist compound. Such residue is preferably selected from a class of compounds of Formula II:



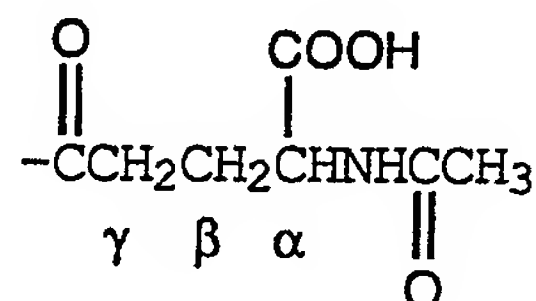
20 wherein each of  $R^{50}$  and  $R^{51}$  may be independently selected from hydrido, alkylcarbonyl, alkoxycarbonyl, alkoxyalkyl, hydroxyalkyl and haloalkyl; and wherein G is selected from hydroxyl, halo, mercapto,  $-OR^{52}$ ,  $-SR^{53}$  and  
 $\diagup \text{NR}^{54} \diagdown$  wherein each of  $R^{52}$ ,  $R^{53}$  and  $R^{54}$  is independently  
 25 selected from hydrido and alkyl; with the proviso that said Formula II compound is selected such that formation of the cleavable amide bond occurs at carbonyl moiety attached at the gamma-position carbon of said Formula II compound.

More preferred are compounds of Formula II wherein each G is hydroxy.

A more highly preferred class of compounds within Formula II consists of those compounds wherein each G is hydroxy; wherein R<sup>50</sup> is hydrido; and wherein R<sup>51</sup> is selected from

$\begin{array}{c} \text{O} \\ || \\ -\text{CR}^{55} \end{array}$  wherein R<sup>55</sup> is selected from methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, neopentyl, n-hexyl and chloromethyl.

A most highly preferred compound of Formula II is N-acetyl- $\gamma$ -glutamic acid which provides a residue for the second component of a conjugate of the invention as shown below:



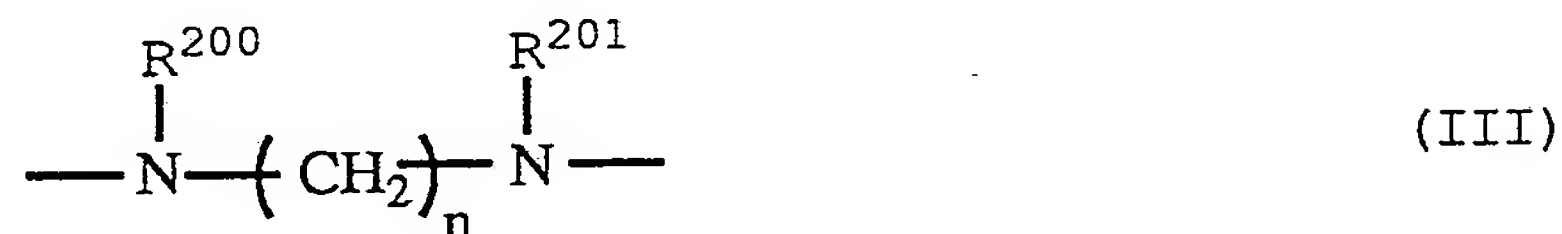
The phrase "terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino terminal moiety" characterizes a structural requirement for selection of a suitable angiotensin II antagonist compound as the "active" first residue of a conjugate of the invention. Such terminal amino moiety must be available to react with a terminal carboxylic moiety of the cleavable second residue to form a kidney-enzyme-specific hydrolyzable bond.

In one embodiment of the invention, the first component used to form a conjugate of the invention provides a first residue derived from an AII antagonist compound

containing a terminal primary or secondary amino moiety. Examples of such terminal amino moiety are amino and linear or branched aminoalkyl moieties containing linear or branched alkyl groups such as aminomethyl, aminoethyl, aminopropyl, aminoisopropyl, aminobutyl, aminosecbutyl, aminoisobutyl, aminotertbutyl, aminopentyl, aminoisopentyl and aminoneopentyl.

In another embodiment of the invention, the first component used to form the conjugate of the invention provides a first residue derived from an AII antagonist compound containing a moiety convertible to a primary or secondary amino terminal moiety. An example of a moiety convertible to an amino terminal moiety is a carboxylic acid group reacted with hydrazine so as to convert the acid moiety to carboxylic acid hydrazide. The hydrazide moiety thus contains the terminal amino moiety which may then be further reacted with the carboxylic acid containing residue of the second component to form a hydrolyzable amide bond. Such hydrazide moiety thus constitutes a "linker" group between the first and second components of a conjugate of the invention.

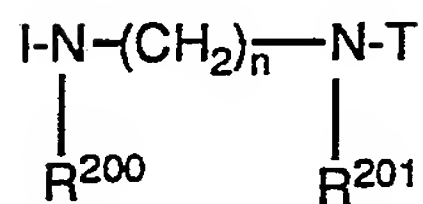
Suitable linker groups may be provided by a class of diamino-terminated linker groups based on hydrazine as defined by Formula III:



wherein each of  $\text{R}^{200}$  and  $\text{R}^{201}$  may be independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, alkoxyalkyl, hydroxyalkyl, aralkyl, aryl, haloalkyl, amino, monoalkylamino, dialkylamino, cyanoamino, carboxyalkyl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; and wherein  $n$  is

zero or a number selected from three through seven, inclusive. In Table I there is shown a class of specific examples of diamino-terminated linker groups within Formula III, identified as Linker Nos. 1-73. These linker groups would be suitable to form a conjugate between a carbonyl moiety of an AII antagonist (designated as "I") and a carbonyl moiety of a carbonyl terminated second residue such as the carbonyl moiety attached to the gamma carbon of a glutamyl residue (designated as "T").

10

TABLE I

I = inhibitor  
T = acetyl- $\gamma$ -glutamyl

LINKER NO.	n	R <sup>200</sup>	R <sup>201</sup>
1	0	H	H
2	0	CH <sub>3</sub>	H
3	0	C <sub>2</sub> H <sub>5</sub>	H
4	0	C <sub>3</sub> H <sub>7</sub>	H
5	0	CH(CH <sub>3</sub> ) <sub>2</sub>	H
6	0	C <sub>4</sub> H <sub>9</sub>	H
7	0	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>3</sub>	H
8	0	C(CH <sub>3</sub> ) <sub>3</sub>	H
9	0	C <sub>5</sub> H <sub>9</sub>	H
10	0	C <sub>6</sub> H <sub>11</sub> (cyclo)	H
11	0	C <sub>6</sub> H <sub>5</sub>	H



LINKER NO.	n	R <sup>200</sup>	R <sup>201</sup>
12	0	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	H
13	0	H	CH <sub>3</sub>
14	0	H	C <sub>2</sub> H <sub>5</sub>
15	0	H	C <sub>3</sub> H <sub>7</sub>
16	0	H	CH(CH <sub>3</sub> ) <sub>2</sub>
17	0	H	C <sub>4</sub> H <sub>9</sub>
18	0	H	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>3</sub>
19	0	H	C(CH <sub>3</sub> ) <sub>3</sub>
20	0	H	C <sub>5</sub> H <sub>9</sub>
21	0	H	C <sub>6</sub> H <sub>13</sub>
22	0	H	C <sub>6</sub> H <sub>5</sub>
23	0	H	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>
24	0	H	C <sub>6</sub> H <sub>11</sub> (cyclo)
25	0	C <sub>6</sub> H <sub>13</sub>	H
26	0	CH <sub>3</sub>	CH <sub>3</sub>
27	0	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>

**SUBSTITUTE SHEET**

LINKER NO.	n	R <sup>200</sup>	R <sup>201</sup>
28	0	C <sub>3</sub> H <sub>7</sub>	C <sub>3</sub> H <sub>7</sub>
29	0	CH(CH <sub>3</sub> ) <sub>2</sub>	CH(CH <sub>3</sub> ) <sub>2</sub>
30	0	C <sub>4</sub> H <sub>9</sub>	C <sub>4</sub> H <sub>9</sub>
31	0	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>3</sub>	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>3</sub>
32	0	C(CH <sub>3</sub> ) <sub>3</sub>	C(CH <sub>3</sub> ) <sub>3</sub>
33	0	C <sub>5</sub> H <sub>9</sub>	C <sub>5</sub> H <sub>9</sub>
34	0	C <sub>6</sub> H <sub>13</sub>	C <sub>6</sub> H <sub>13</sub>
35	0	C <sub>6</sub> H <sub>11</sub> (cyclo)	C <sub>6</sub> H <sub>11</sub> (cyclo)
36	0	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>
37	0	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>
38	3	H	H
39	3	CH <sub>3</sub>	H
40	3	H	CH <sub>3</sub>
41	3	C <sub>6</sub> H <sub>5</sub>	H
42	3	H	C <sub>6</sub> H <sub>5</sub>

**SUBSTITUTE SHEET**

43

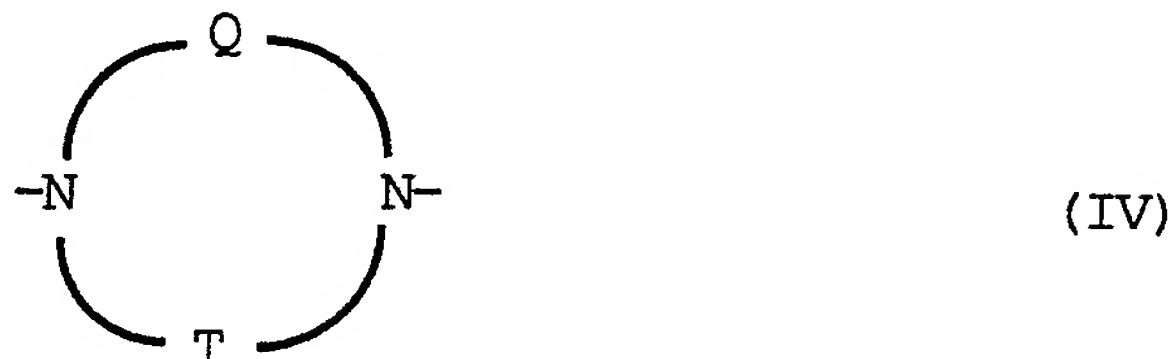
LINKER NO.	n	R <sup>200</sup>	R <sup>201</sup>
43	3	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>
44	3	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>
45	3	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	H
46	3	H	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>
47	4	H	H
48	4	CH <sub>3</sub>	H
49	4	H	CH <sub>3</sub>
50	4	C <sub>6</sub> H <sub>5</sub>	H
51	4	H	C <sub>6</sub> H <sub>5</sub>
52	4	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>
53	4	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>
54	4	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	H
55	4	H	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>
56	5	H	H
57	5	CH <sub>3</sub>	H
58	5	H	CH <sub>3</sub>

**SUBSTITUTE SHEET**

LINKER NO.	n	R <sup>200</sup>	R <sup>201</sup>
59	5	C <sub>6</sub> H <sub>5</sub>	H
60	5	H	C <sub>6</sub> H <sub>5</sub>
61	5	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>
62	5	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>
63	5	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	H
64	5	H	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>
65	6	H	H
66	6	CH <sub>3</sub>	H
67	6	H	CH <sub>3</sub>
68	6	C <sub>6</sub> H <sub>5</sub>	H
69	6	H	C <sub>6</sub> H <sub>5</sub>
70	6	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>
71	6	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>
72	6	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	H
73	6	H	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>

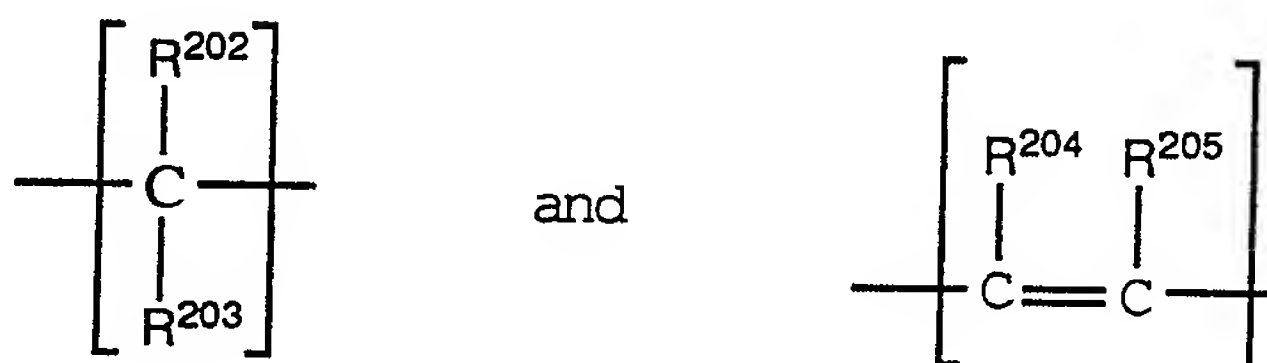
**SUBSTITUTE SHEET**

Another class of suitable diamino terminal linker groups is defined by Formula IV:



5

wherein each of Q and T is one or more groups independently selected from



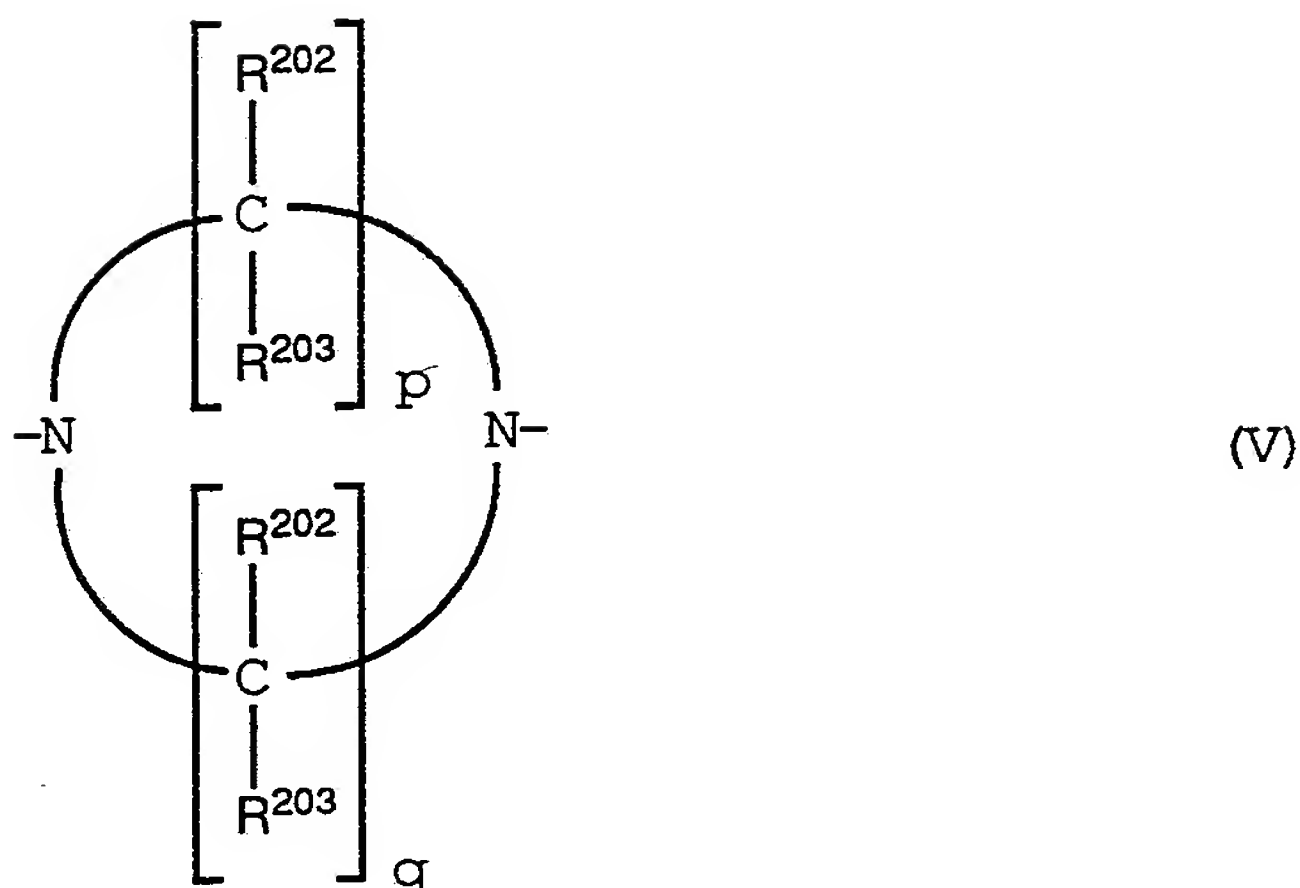
10

wherein each of R<sup>202</sup> through R<sup>205</sup> is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, aryloxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl and alkynyl.

15

A preferred class of linker groups within Formula IV is defined by Formula V:

20

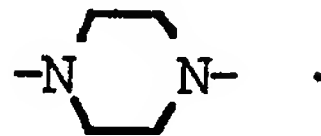


wherein each of  $R^{202}$  and  $R^{203}$  is independently selected from hydrido, hydroxy, alkyl, phenalkyl, phenyl, alkoxy, benzyloxy, phenoxy, alkoxyalkyl, hydroxyalkyl, halo, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl and alkanoyl; and wherein each of  $p$  and  $q$  is a number independently selected from one through six, inclusive; with the proviso that when each of  $R^{202}$  and  $R^{203}$  is selected from halo, hydroxy, amino, monoalkylamino and dialkylamino, then the carbon to which  $R^{202}$  or  $R^{203}$  is attached in Formula V is not adjacent to a nitrogen atom of Formula V.

A more preferred class of linker groups of Formula V consists of divalent radicals wherein each of  $R^{202}$  and  $R^{203}$  is independently selected from hydrido, hydroxy, alkyl, alkoxy, amino, monoalkylamino, carboxy, carboxyalkyl and alkanoyl; and wherein each of  $p$  and  $q$  is a number independently selected from two through four, inclusive. Even more preferred are linker groups wherein each of  $R^{202}$  and  $R^{203}$  is independently selected from hydrido, amino, monoalkylamino and carboxyl; and wherein each of  $p$  and  $q$  is independently selected from the numbers two and three. Most preferred is a linker group wherein each of  $R^{202}$  and  $R^{203}$  is hydrido; and wherein each of  $p$  and  $q$  is two; such most preferred linker



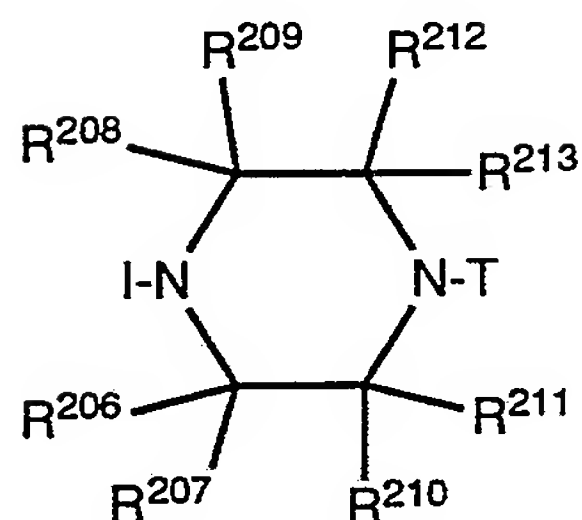
group is derived from a piperazinyl group and has the structure



5

In Table II there is shown a class of specific examples of cyclized, diamino-terminated linker groups within Formula V. These linker groups, identified as Linker Nos. 74-10 95, would be suitable to form a conjugate between a carbonyl moiety of an AII antagonist (designated as "I") and a carbonyl moiety of carbonyl terminated second residue such as the carbonyl moiety attached to the gamma carbon of a glutamyl residue (designated as "T").

15

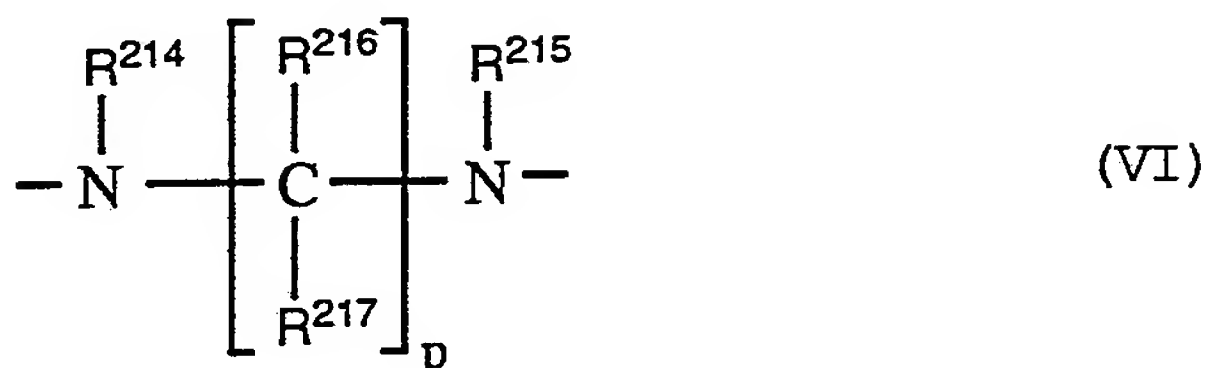
TABLE II

I = inhibitor  
T = acetyl- $\gamma$ -glutamyl

LINKER NO.	R <sup>206</sup>	R <sup>207</sup>	R <sup>208</sup>	R <sup>209</sup>	R <sup>210</sup>	R <sup>211</sup>	R <sup>212</sup>	R <sup>213</sup>
74	H	H	H	H	H	H	H	H
75	CH <sub>3</sub>	H	H	H	H	H	H	H
76	H	H	H	H	CH <sub>3</sub>	H	H	H
77	CH <sub>3</sub>	H	H	H	CH <sub>3</sub>	H	H	H
78	CH <sub>3</sub>	H	CH <sub>3</sub>	H	H	H	H	H
79	CH <sub>3</sub>	H	H	H	H	H	CH <sub>3</sub>	H
80	CH <sub>3</sub>	CH <sub>3</sub>	H	H	H	H	H	H
81	H	H	H	H	CH <sub>3</sub>	CH <sub>3</sub>	H	H
82	CH <sub>3</sub>	CH <sub>3</sub>	H	H	CH <sub>3</sub>	CH <sub>3</sub>	H	H
83	CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	H	H	H	H

LINKER NO.	R206	R207	R208	R209	R210	R211	R212	R213
84	CH <sub>3</sub>	CH <sub>3</sub>	H	H	H	H	CH <sub>3</sub>	CH <sub>3</sub>
85	H	H	H	H	CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>
86	C <sub>6</sub> H <sub>5</sub>	H	H	H	H	H	H	H
87	H	H	H	H	C <sub>6</sub> H <sub>5</sub>	H	H	H
88	C <sub>6</sub> H <sub>5</sub>	H	H	H	C <sub>6</sub> H <sub>5</sub>	H	H	H
89	C <sub>6</sub> H <sub>5</sub>	H	H	H	H	H	C <sub>6</sub> H <sub>5</sub>	H
90	C <sub>6</sub> H <sub>5</sub>	H	C <sub>6</sub> H <sub>5</sub>	H	H	H	H	H
91	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	H	H	H	H	H	H	H
92	H	H	H	H	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	H	H	H
93	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	H	H	H	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	H	H	H
94	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	H	H	H	H	H	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	H
95	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	H	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	H	H	H	H	H

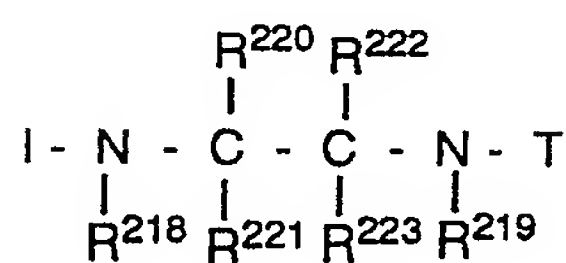
Another class of suitable diamino terminal linker groups is defined by Formula VI:



5 wherein each of R<sup>214</sup> through R<sup>217</sup> is independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, hydroxyalkyl, alkoxyalkyl, aralkyl, aryl, haloalkyl, amino, monoalkylamino, dialkylamino, cyanoamino, carboxyalkyl, 10 alkylsulfinio, alkylsulfonyl, arylsulfinyl and arylsulfonyl; and wherein p is a number selected from one through six inclusive.

A preferred class of linker groups within Formula 15 VI consists of divalent radicals wherein each of R<sup>214</sup> and R<sup>215</sup> is hydrido; wherein each of R<sup>216</sup> and R<sup>217</sup> is independently selected from hydrido, alkyl, phenalkyl, phenyl, alkoxyalkyl, hydroxyalkyl, haloalkyl and carboxyalkyl; and wherein p is two or three. A more preferred class of linker groups within 20 Formula VI consists of divalent radicals wherein each of R<sup>214</sup> and R<sup>215</sup> is hydrido; wherein each of R<sup>216</sup> and R<sup>217</sup> is independently selected from hydrido and alkyl; and wherein p is two. A specific example of a more preferred linker within Formula VI is the divalent radical ethylenediamino. In Table 25 III there is shown a class of specific examples of diamino-terminated linker groups within Formula VI. These linker groups, identified as Linker Nos. 96-134, would be suitable to

form a conjugate between a carbonyl moiety of an AII antagonist (designated as "I") and a carbonyl moiety of carbonyl terminated second residue such as the carbonyl moiety attached to the gamma carbon of a glutamyl residue (designated as "T").

TABLE III

I = inhibitor  
G = acetyl- $\gamma$ -glutamyl

LINKER NO.	R <sup>218</sup>	R <sup>219</sup>	R <sup>220</sup>	R <sup>221</sup>	R <sup>222</sup>	R <sup>223</sup>
96	H	H	H	H	H	H
97	H	H	H	H	H	CH <sub>3</sub>
98	H	H	H	CH <sub>3</sub>	H	H
99	H	H	H	CH <sub>3</sub>	H	CH <sub>3</sub>
100	CH <sub>3</sub>	H	H	H	H	H
101	H	CH <sub>3</sub>	H	H	H	H
102	H	H	H	H	CH <sub>3</sub>	CH <sub>3</sub>
103	H	H	CH <sub>3</sub>	CH <sub>3</sub>	H	H

LINKER NO.	R <sup>218</sup>	R <sup>219</sup>	R <sup>220</sup>	R <sup>221</sup>	R <sup>222</sup>	R <sup>223</sup>
104	CH <sub>3</sub>	CH <sub>3</sub>	H	H	H	H
105	H	H	H	H	H	C <sub>6</sub> H <sub>5</sub>
106	H	H	H	C <sub>6</sub> H <sub>5</sub>	H	H
107	H	H	H	C <sub>6</sub> H <sub>5</sub>	H	C <sub>6</sub> H <sub>5</sub>
108	C <sub>6</sub> H <sub>5</sub>	H	H	H	H	H
109	H	C <sub>6</sub> H <sub>5</sub>	H	H	H	H
110	H	H	H	H	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>
111	H	H	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	H	H
112	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	H	H	H	H
113	H	H	H	H	H	C <sub>2</sub> H <sub>5</sub>
114	H	H	H	C <sub>2</sub> H <sub>5</sub>	H	H
115	H	H	H	C <sub>2</sub> H <sub>5</sub>	H	C <sub>2</sub> H <sub>5</sub>
116	C <sub>2</sub> H <sub>5</sub>	H	H	H	H	H
117	H	C <sub>2</sub> H <sub>5</sub>	H	H	H	H
118	H	H	H	H	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>

**SUBSTITUTE SHEET**



LINKER NO.	R <sup>218</sup>	R <sup>219</sup>	R <sup>220</sup>	R <sup>221</sup>	R <sup>222</sup>	R <sup>223</sup>
119	H	H	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	H	H
120	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	H	H	H	H
121	CH <sub>3</sub>	H	C <sub>6</sub> H <sub>5</sub>	H	H	H
122	CH <sub>3</sub>	H	H	H	C <sub>6</sub> H <sub>5</sub>	H
123	H	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	H	H	H
124	H	CH <sub>3</sub>	H	H	C <sub>6</sub> H <sub>5</sub>	H
125	CH <sub>3</sub>	CH <sub>3</sub>	H	C <sub>6</sub> H <sub>5</sub>	H	H
126	CH <sub>3</sub>	CH <sub>3</sub>	H	H	H	C <sub>6</sub> H <sub>5</sub>
127	H	H	H	H	H	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>
128	H	H	H	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	H	H
129	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	H	H	H	H	H
130	H	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	H	H	H	H
131	CH <sub>3</sub>	H	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	H	H	H
132	CH <sub>3</sub>	H	H	H	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	H
133	H	CH <sub>3</sub>	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	H	H	H

SUBSTITUTE SHEET

LINKER NO.	R <sup>218</sup>	R <sup>219</sup>	R <sup>220</sup>	R <sup>221</sup>	R <sup>222</sup>	R <sup>223</sup>
---------------	------------------	------------------	------------------	------------------	------------------	------------------

134	H	CH <sub>3</sub>	H	H	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	H
-----	---	-----------------	---	---	---	---

The term "hydrido" denotes a single hydrogen atom (H) which may be attached, for example, to a carbon atom to form a hydrocarbyl group or attached to an oxygen atom to form an hydroxyl group. Where the term "alkyl" is used, either alone or within other terms such as "haloalkyl" and "hydroxyalkyl", the term "alkyl" embraces linear or branched radicals having one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about ten carbon atoms. Most preferred are lower alkyl radicals having one to about five carbon atoms. The term "cycloalkyl" embraces cyclic radicals having three to about ten ring carbon atoms, preferably three to about six carbon atoms, such as cyclopropyl and cyclobutyl. The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with one or more halo groups, preferably selected from bromo, chloro and fluoro. Specifically embraced by the term "haloalkyl" are monohaloalkyl, dihaloalkyl and polyhaloalkyl groups. A monohaloalkyl group, for example, may have either a bromo, a chloro, or a fluoro atom within the group. Dihalalkyl and polyhaloalkyl groups may be substituted with two or more of the same halo groups, or may have a combination of different halo groups. A dihaloalkyl group, for example, may have two fluoro atoms, such as difluoromethyl and difluorobutyl groups, or two chloro atoms, such as a dichloromethyl group, or one fluoro atom and one chloro atom, such as a fluoro-chloromethyl group. Examples of a polyhaloalkyl are trifluoromethyl, 1,1-difluoroethyl, 2,2,2-trifluoroethyl, perfluoroethyl and 2,2,3,3-tetrafluoropropyl

groups. The term "difluoroalkyl" embraces alkyl groups having two fluoro atoms substituted on any one or two of the alkyl group carbon atoms. Preferably, when the difluoroalkyl group is attached at the triazole ring R<sup>1</sup> and R<sup>2</sup> positions of

5 Formula I, the two fluoro atoms are substituted on the carbon atom which is attached directly to the triazole ring. Such preferred difluoroalkyl group may be characterized as an "alpha-carbon difluoro-substituted difluoroalkyl group" The terms "alkylol" and "hydroxyalkyl" embrace linear or branched

10 alkyl groups having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl groups. The term "alkenyl" embraces linear or branched radicals having two to about twenty carbon atoms, preferably three to about ten carbon atoms, and containing at least one carbon-carbon

15 double bond, which carbon-carbon double bond may have either cis or trans geometry within the alkenyl moiety. The term "alkynyl" embraces linear or branched radicals having two to about twenty carbon atoms, preferably two to about ten carbon atoms, and containing at least one carbon-carbon triple bond.

20 The term "cycloalkenyl" embraces cyclic radicals having three to about ten ring carbon atoms including one or more double bonds involving adjacent ring carbons. The terms "alkoxy" and "alkoxyalkyl" embrace linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon

25 atoms, such as methoxy group. The term "alkoxyalkyl" also embraces alkyl radicals having two or more alkoxy groups attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl groups. The "alkoxy" or "alkoxyalkyl" radicals may be further substituted with one or

30 more halo atoms, such as fluoro, chloro or bromo, to provide haloalkoxy or haloalkoxyalkyl groups. The term "alkylthio" embraces radicals containing a linear or branched alkyl group, of one to about ten carbon atoms attached to a divalent sulfur atom, such as a methythio group. The term "aryl" embraces

35 aromatic radicals such as phenyl, naphthyl and biphenyl. The

term "aralkyl" embraces aryl-substituted alkyl radicals such as benzyl, diphenylmethyl, triphenylmethyl, phenylethyl, phenylbutyl and diphenylethyl. The terms "benzyl" and "phenylmethyl" are interchangeable. The terms "aryloxy" and "arylthio" denote radical respectively, aryl groups having an oxygen or sulfur atom through which the radical is attached to a nucleus, examples of which are phenoxy and phenylthio. The terms "sulfinyl" and "sulfonyl", whether used alone or linked to other terms, denotes respectively divalent radicals SO and SO<sub>2</sub>. The term "aralkoxy", alone or within another term, embraces an aryl group attached to an alkoxy group to form, for example, benzyloxy. The term "acyl" whether used alone, or within a term such as acyloxy, denotes a radical provided by the residue after removal of hydroxyl from an organic acid, examples of such radical being acetyl and benzoyl. The term "heteroaryl" embraces aromatic ring systems containing one or two hetero atoms selected from oxygen, nitrogen and sulfur in a ring system having five or six ring members, examples of which are thienyl, furanyl, pyridinyl, thiazolyl, pyrimidyl and isoxazolyl. Such heteroaryl may be attached as a substituent through a carbon atom of the heteroaryl ring system, or may be attached through a carbon atom of a moiety substituted on a heteroaryl ring-member carbon atom, for example, through the methylene substituent of imidazolemethyl moiety. Also, such heteroaryl may be attached through a ring nitrogen atom as long as aromaticity of the heteroaryl moiety is preserved after attachment.

Specific examples of alkyl groups are methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, methylbutyl, dimethylbutyl and neopentyl. Typical alkenyl and alkynyl groups may have one unsaturated bond, such as an allyl group, or may have a plurality or unsaturated bonds, with such plurality of bonds

either adjacent, such as allene-type structures, or in conjugation, or separated by several saturated carbons.

Conjugates of the invention formed from compounds of Formula I have been found to inhibit the action of angiotensin II in mammals. For example, specific biphenylmethyl 1H-substituted-imidazole compounds within Formula I have been evaluated for angiotensin II receptor binding and antihypertensive effects in renal hypertensive rats, as shown in EP #253,310 published 20 January 1988. Thus, conjugates of Formula I are therapeutically useful in methods for treating hypertension by administering to a hypertensive patient a therapeutically-effective amount of a conjugate containing a compound of Formula I, such that the conjugate is hydrolyzed by an enzyme found predominantly in the kidney so as to release an active angiotensin II antagonist species. The phrase "hypertensive patient" means, in this context, a mammalian subject suffering from the effects of hypertension or susceptible to a hypertensive condition if not treated to prevent or control such hypertension.

Included within the invention are conjugates of compounds of Formula I which are tautomeric forms of the described compounds, isomeric forms including diastereoisomers, and the pharmaceutically-acceptable salts thereof. The term "pharmaceutically-acceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically-acceptable. Suitable pharmaceutically-acceptable acid addition salts of compounds of Formula I may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and



phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, example of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, p-hydroxybenzoic, salicylic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, 2-hydroxyethanesulfonic, pantothenic, benzenesulfonic, toluenesulfonic, sulfanilic, mesylic, cyclohexylaminosulfonic, stearic, algenic,  $\beta$ -hydroxy butyric, malonic, galactaric and galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of compounds of Formula I include metallic salts made from aluminium, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. All of these salts may be prepared by conventional means from the corresponding compound of Formula I by reacting, for example, the appropriate acid or base with the compound of Formula I. Also, such pharmaceutical salts may be formed with either a compound of Formula I which is contained in the conjugate, or such salts may be formed with the conjugate itself.

Conjugates of the invention can possess one or more asymmetric carbon atoms and are thus capable of existing in the form of optical isomers as well as in the form of racemic or non-racemic mixtures thereof. The optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes, for example by formation of diastereoisomeric salts by treatment with an optically active acid or base. Examples of appropriate acids are tartaric, diacetyltartaric, dibenzoyltartaric, ditoluoyltartaric and camphorsulfonic acid and then separation of the mixture of



diastereoisomers by crystallization followed by liberation of the optically active bases from these salts. A different process for separation of optical isomers involves the use of a chiral chromatography column optimally chosen to maximize the separation of the enantiomers. Still another available method involves synthesis of covalent diastereoisomeric molecules by reacting conjugates with an optically pure acid in an activated form or an optically pure isocyanate. The synthesized diastereoisomers can be separated by conventional means such as chromatography, distillation, crystallization or sublimation, and then hydrolyzed to deliver the enantiomerically pure compound. The optically active conjugates can likewise be obtained by utilizing optically active starting materials. These isomers may be in the form of a free acid, a free base, an ester or a salt.

Conjugates of the invention may be prepared using precursors of highly active angiotensin II antagonists of Formula I. Examples of lesser active, suitable precursors are acid chloride, esters and amides of angiotensin II antagonists of Formula I. For example, ester precursors of angiotensin II antagonists, such as the methyl ester precursor made in Step 1 of Example 81, may be reacted with hydrazine to provide an amino terminal moiety which then can be reacted with a glutamic acid derivative to form a conjugate of the invention. Such precursors or intermediates themselves may be relatively strong, relatively weak, or inactive as AII antagonists. Also, conjugates of the invention may be prepared using angiotensin II antagonists lacking a reactive terminal amino moiety. Such angiotensin II antagonists, as shown in Example Nos. 78-80 of Table IV, lack a terminal amino moiety. These AII antagonist compounds may be modified as described in

Example Nos. 711 and 712 to contain a terminal acid moiety which then may be connected to a glutamyl residue through a diamino-terminated linker group, such as shown in Tables I-III.

5

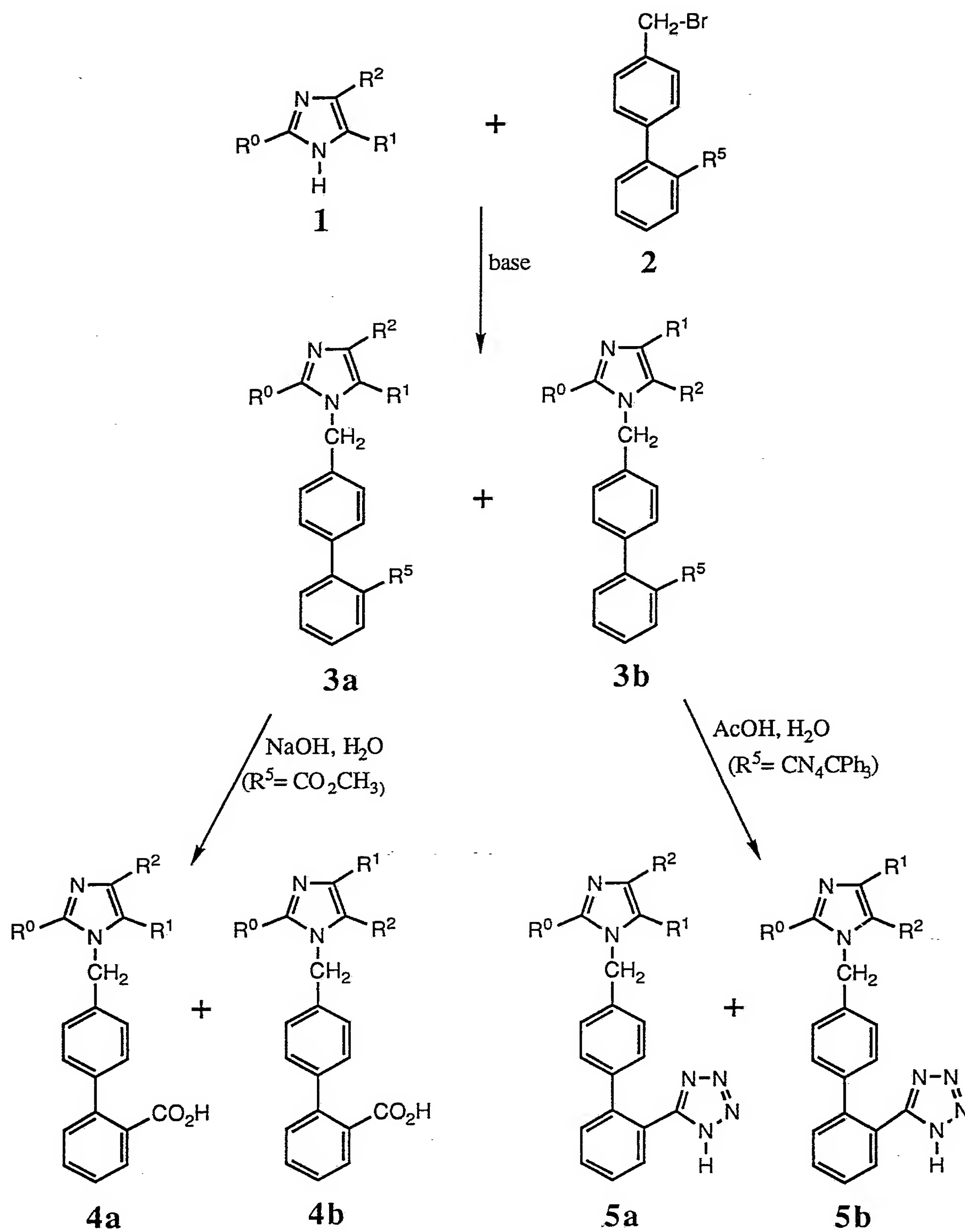
### Synthetic Procedures

Conjugates of the invention are synthesized by  
10 reaction between precursors of the first and second residues. One of such precursors must contain a reactive acid moiety, and the other precursor must contain a reactive amino moiety, so that a conjugate is formed having a cleavable bond. Either precursor of the first and second  
15 residues may contain such reactive acid or amino moieties. Preferably, the precursors of the first residue are angiotensin II antagonists and will contain a reactive amino moiety or a moiety convertible to a reactive amino moiety. Inhibitor compounds lacking a reactive amino  
20 moiety may be chemically modified to provide such reactive amino moiety. Chemical modification of these inhibitor compounds lacking a reactive amino group may be accomplished by reacting an acid or an ester group on an AII antagonist compound with an amino compound having at  
25 least one reactive amino moiety. A suitable amino compound would be a diamino compound such as hydrazine, urea or ethylenediamine. Hydrazine, for example, may be reacted with a carboxylic acid or ester moiety of an AII antagonist compound to form a hydrazide derivative of such AII  
30 antagonist compound.

In the following general Synthetic Procedures, there is described firstly in Scheme I, methods for making suitable angiotensin II antagonists of Formula I for selection as the first component of the conjugate. Then, in Schemes II-VII, there are described general methods for making a conjugate by reacting a first component AII antagonist of Formula I with a cleavable second component represented by N-acetyl- $\gamma$ -glutamic acid.

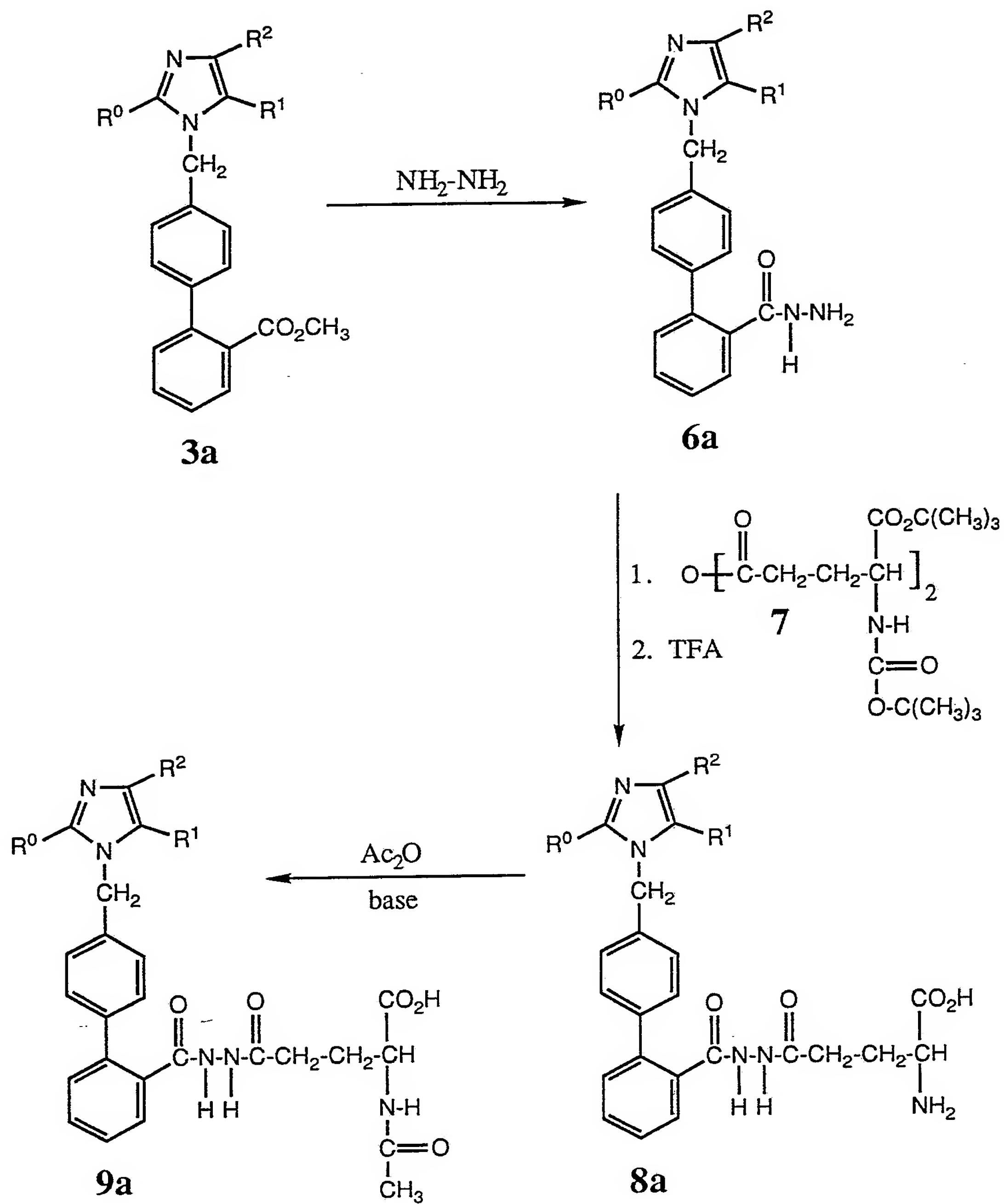
10

## Scheme I



Synthetic Scheme I shows the coupling reaction of trisubstituted imidazoles 1 with the appropriate alkylating reagent 2. In the first step, 1 and 2 are reacted in  
5 dimethylformamide (DMF) in the presence of base, such as cesium carbonate, and a dehydrating agent, such as molecular sieves, to give a mixture of coupled regioisomers 3a and 3b. The isomer mixture may be converted to mixtures of the corresponding acids 4a and 4b or tetrazoles 5a and 5b. Or,  
10 the isomers 3a and 3b may be separated by chromatographic methods, and each isomer may be reacted with the appropriate reagent to provide the acid- or tetrazole-substituted end product.

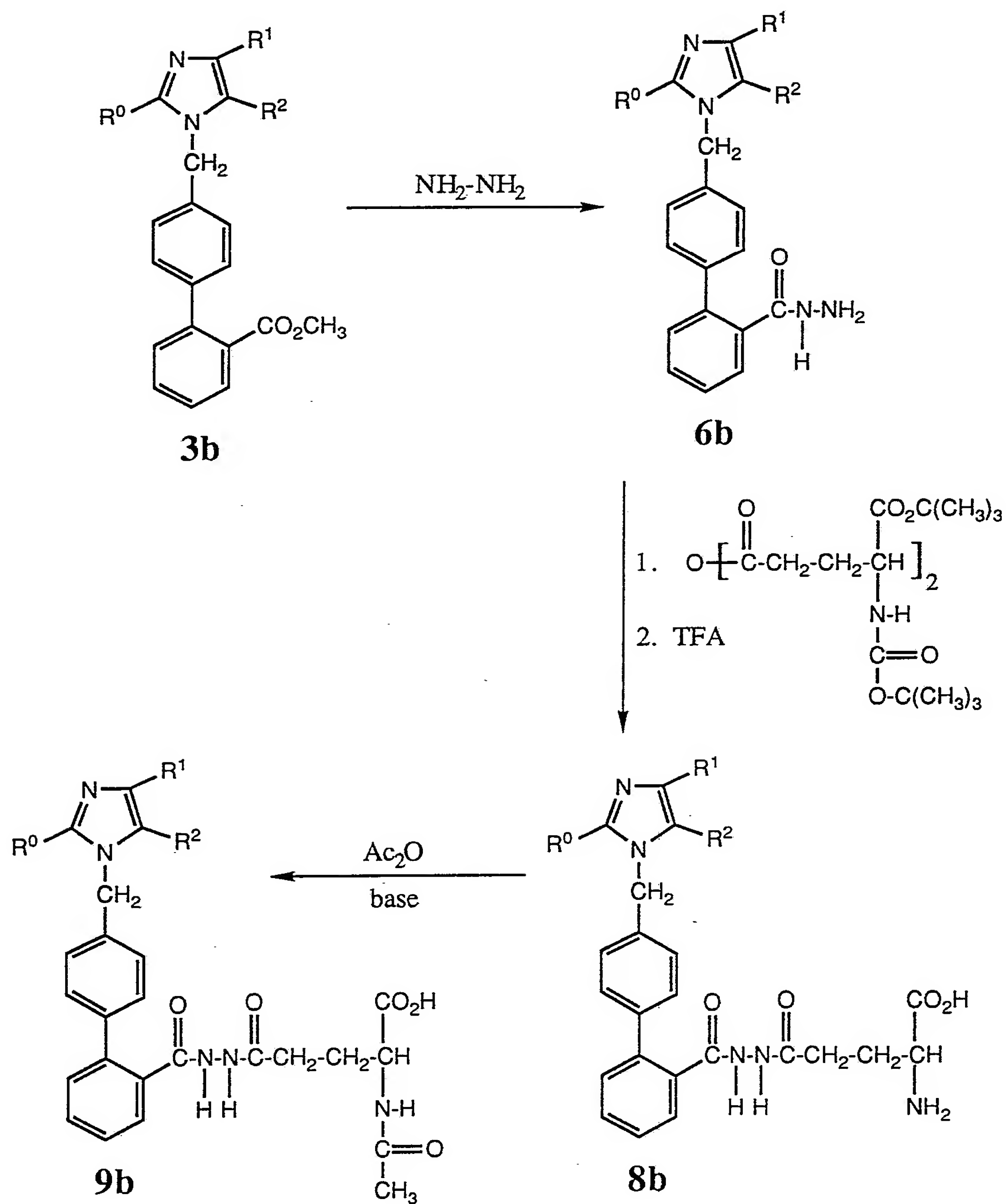
## Scheme II



Synthetic Scheme II shows the preparation of the renal-selective angiotensin II antagonists by coupling  $\gamma$ -glutamic acid with one of the angiotensin II antagonist regiosiomers 3a (the synthesis of the other regioisomer is shown in Scheme III); the biphenyl R<sup>5</sup> acid moiety of the AII antagonist is coupled to the  $\gamma$ -acid moiety of glutamic acid via an hydrazine linker. In step 1, the methyl ester of the AII antagonist 3a is converted to the hydrazide 6a by the action of hydrazine. In step 2, the hydrazide 6a is first reacted with the symmetrical anhydride of the protected  $\gamma$ -glutamic acid 7 and subsequently reacted with trifluoroacetic acid (TFA) to give the deprotected coupled material 8a. In Step 3, the free amino group of 8a is acetylated with acetic anhydride in the presence of base to give the renal-selective angiotensin II antagonist 9a.

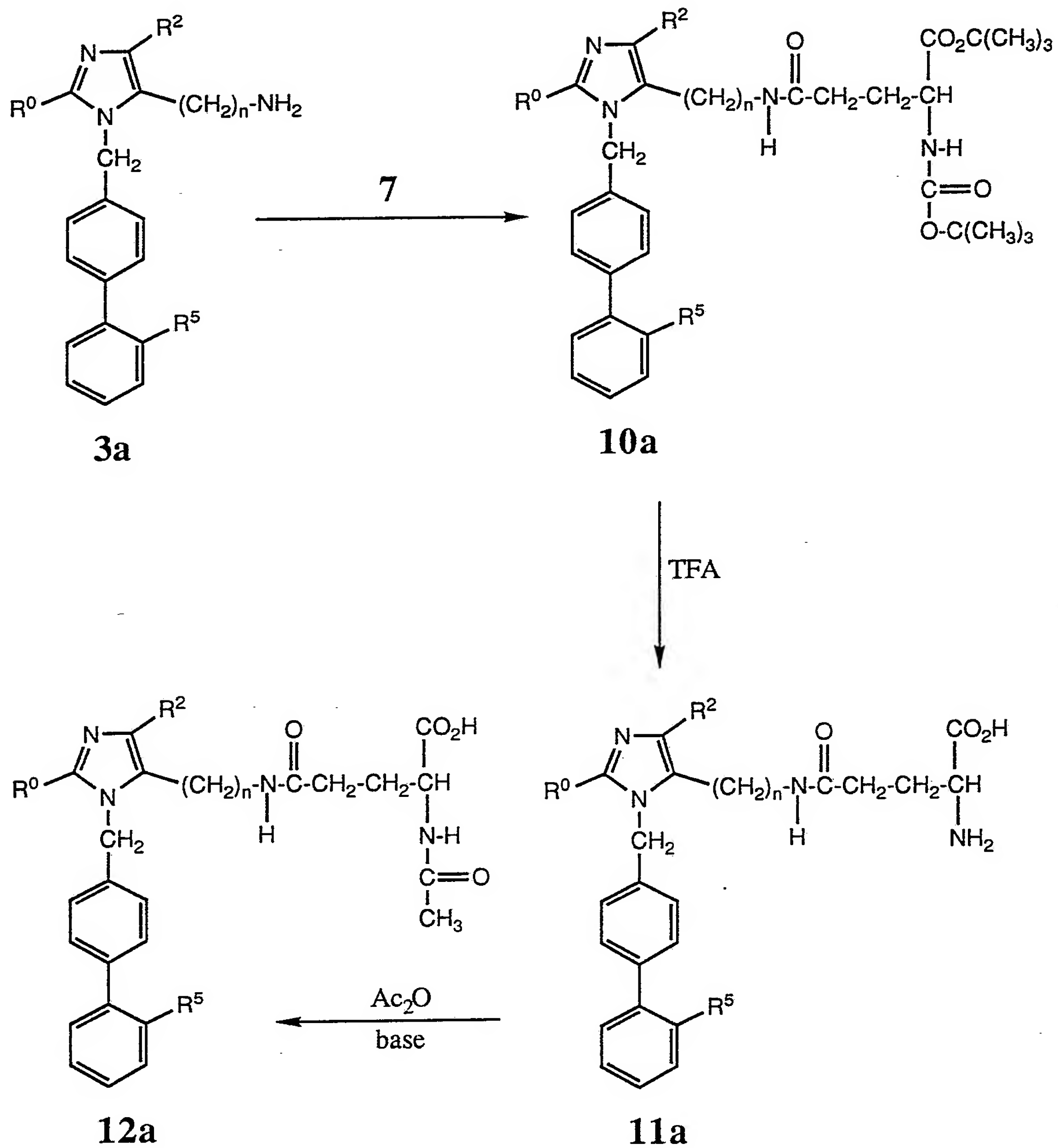


## Scheme III



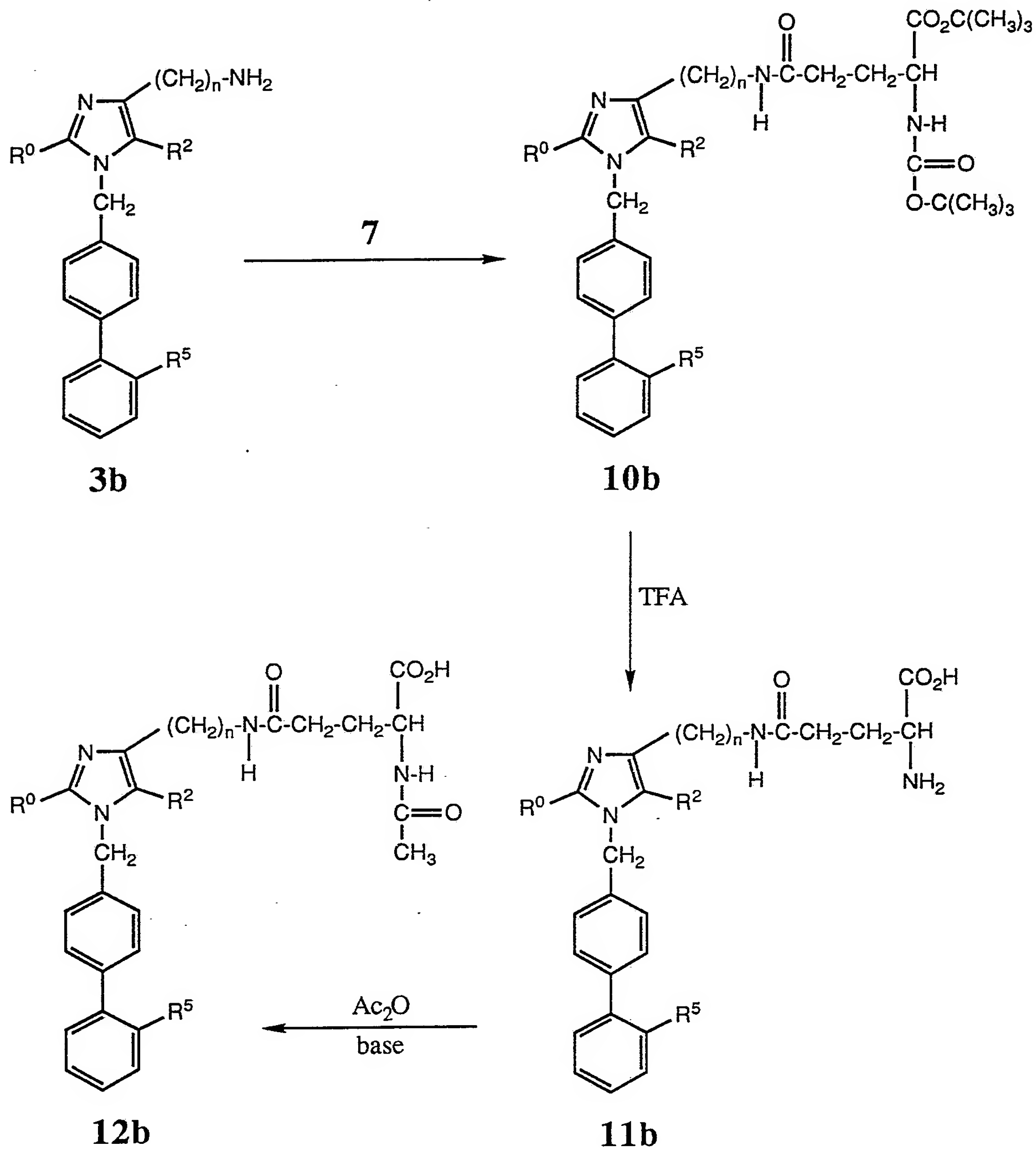
Synthetic Scheme III shows the preparation of renal-selective angiotensin II antagonists by coupling  $\gamma$ -glutamic acid with one of the angiotensin II antagonist regioisomers 3b (the synthesis of the other regioisomer is shown in Scheme II); the biphenyl R<sup>5</sup> acid moiety of the AII antagonist is coupled to the  $\gamma$ -acid moiety of glutamic acid via an hydrazine linker. In step 1, the methyl ester of the AII antagonist 3b is converted to the hydrazide 6b by the action of hydrazine. In step 2, the hydrazide 6b is first reacted with the symmetrical anhydride of the protected  $\gamma$ -glutamic acid 7 and subsequently reacted with TFA to give the deprotected coupled material 8b. In step 3, the free amino group of 8b is acetylated with acetic anhydride in the presence of base to give the renal-selective angiotensin II antagonist 9b.

## Scheme IV



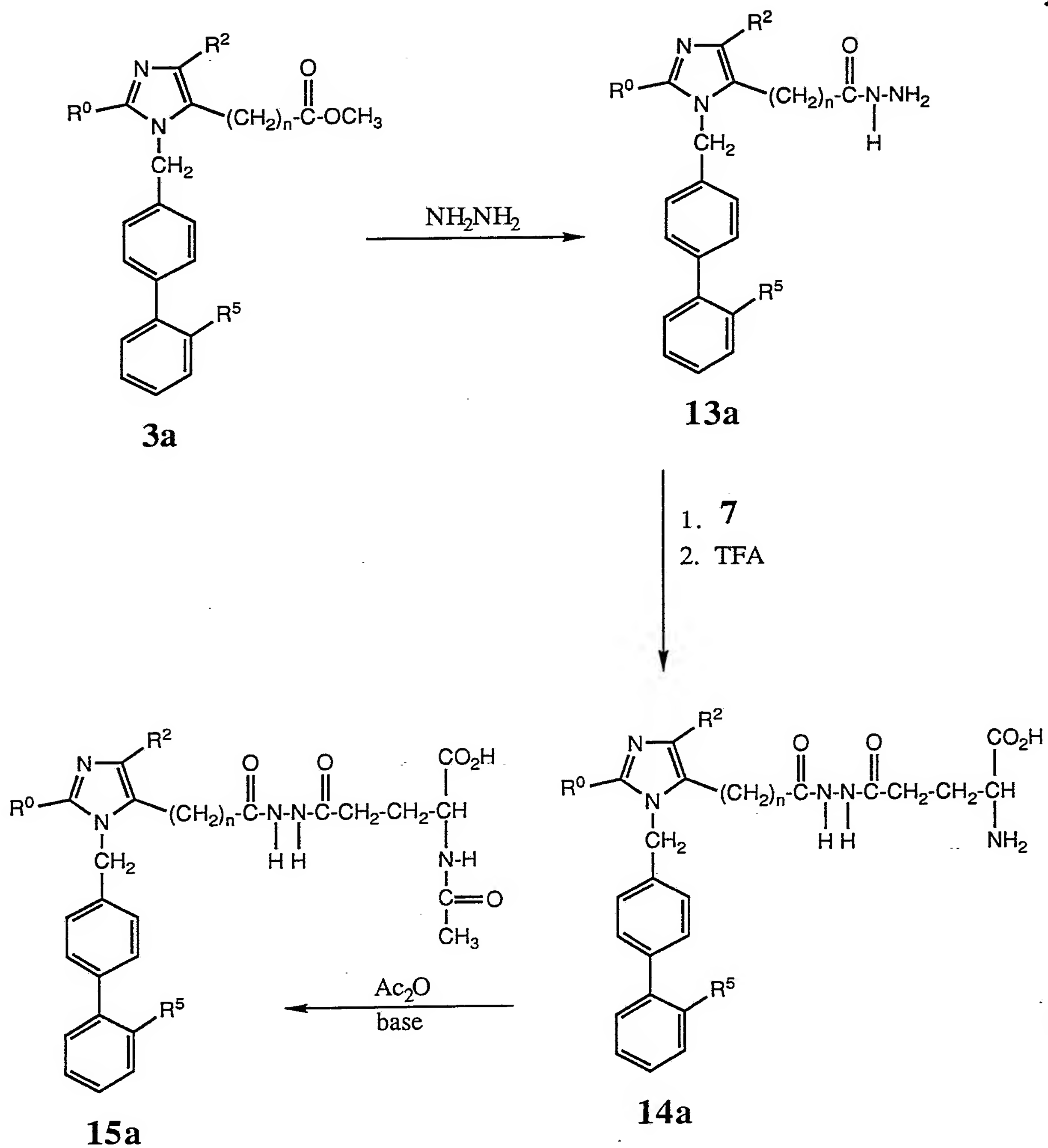
Synthetic Scheme IV shows the preparation of renal-selective angiotensin II antagonists by coupling  $\gamma$ -glutamic acid with one of the angiotensin II antagonist regioisomers 3a which contains an amino moiety in the imidazole R<sup>1</sup> group (the synthesis of the other regioisomer is shown in Scheme V). In step 1, the AII antagonist 3a is reacted with the symmetrical anhydride of the protected  $\gamma$ -glutamic acid 7 to give 10a. In step 2, the protected material 10a is reacted with TFA to give the deprotected coupled material 11a. In step 3, the free amino compound 11a is acetylated with acetic anhydride in the presence of base to give the renal-selective angiotensin II antagonist 12a.

## Scheme V



Synthetic Scheme V shows the preparation of renal-selective angiotensin II antagonists by coupling  $\gamma$ -glutamic acid with one of the angiotensin II antagonist regioisomers 3b which contains an amino moiety in the imidazole R<sup>1</sup> group (the synthesis of the other regioisomer is shown in Scheme IV). In step 1, the AII antagonist 3b is reacted with the symmetrical anhydride of the protected  $\gamma$ -glutamic acid 7 to give 10b. In step 2, the protected material 10b is reacted with TFA to give the deprotected coupled material 11b. In step 3, the free amino compound 11b is acetylated with acetic anhydride in the presence of base to give the renal-selective angiotensin II antagonist 12b.

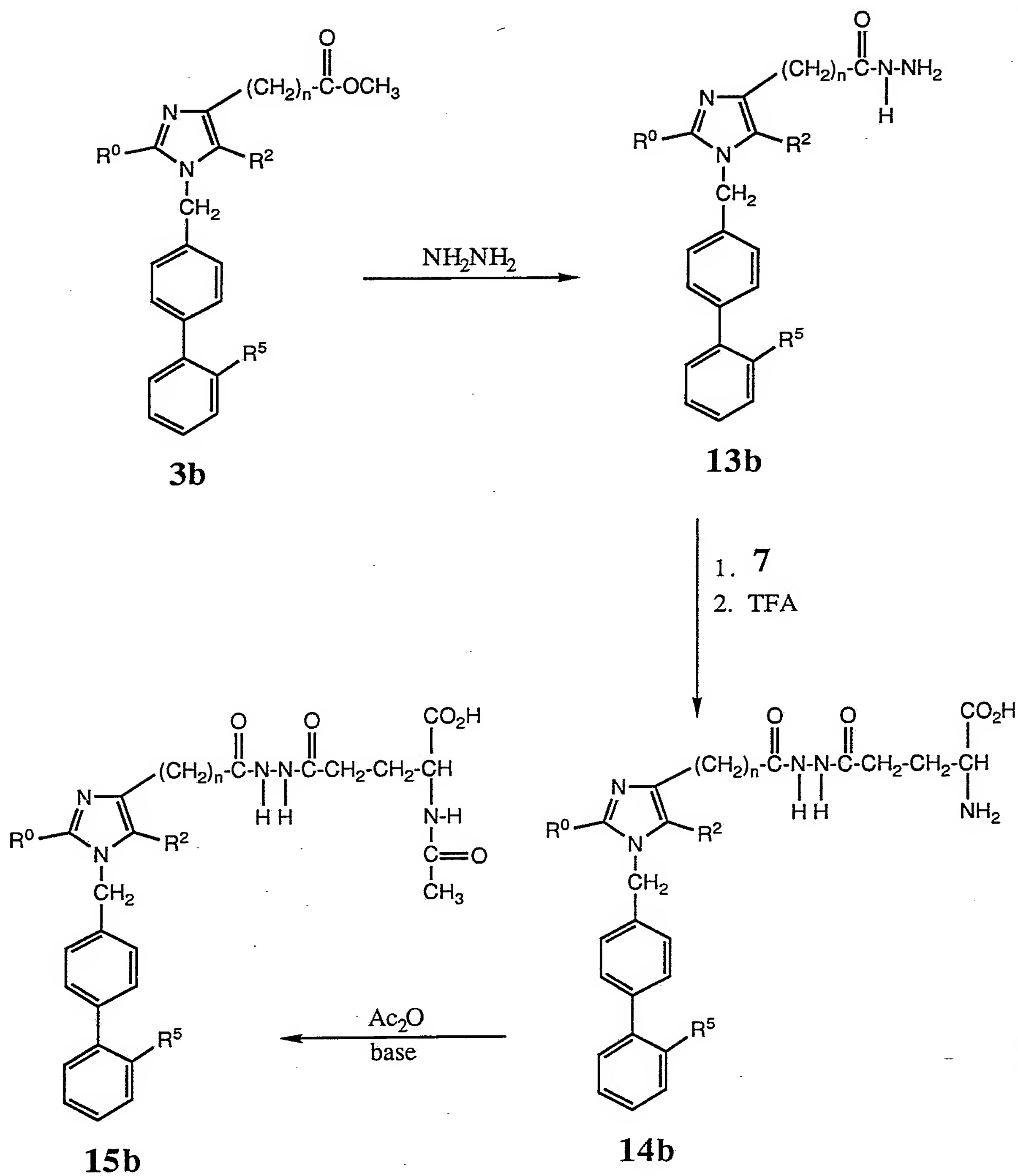
## Scheme VI





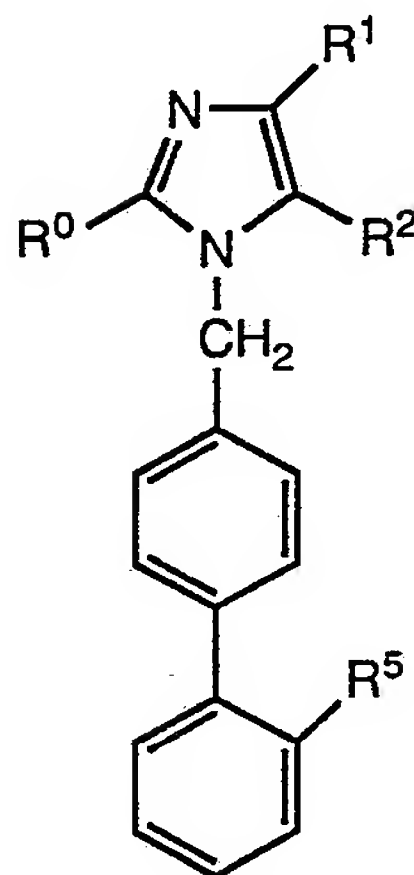
Synthetic Scheme VI shows the preparation of renal-selective angiotensin II antagonists by coupling  $\gamma$ -glutamic acid with one of the angiotensin II antagonist regioisomers 3a which contains an acid moiety in the imidazole R<sup>1</sup> group (the synthesis of the other regioisomer is shown in Scheme VII); the imidazole R<sup>1</sup> acid moiety of the AII antagonist is coupled to the  $\gamma$ -acid moiety of glutamic acid via an hydrazine linker. In step 1, the methyl ester of the AII antagonist 3a is converted to the hydrazide 13a by the action of hydrazine. In step 2, the hydrazide 13a is first reacted with the symmetrical anhydride of the protected  $\gamma$ -glutamic acid 7 and subsequently reacted with TFA to give the deprotected coupled material 14a. In step 3, the free amino group of 14a is acetylated with acetic anhydride in the presence of base to give the renal-selective angiotensin II antagonist 15a.

## Scheme VII





Synthetic Scheme VII shows the preparation of renal-selective angiotensin II antagonists by coupling  $\gamma$ -glutamic acid with one of the angiotensin II antagonist regioisomers 3b which contains an acid moiety in the imidazole R<sup>1</sup> group (the synthesis of the other isomer is shown in Scheme VII); the imidazole R<sup>1</sup> acid moiety of the AII antagonist is coupled to the  $\gamma$ -acid moiety of glutamic acid via an hydrazine linker. In step 1, the methyl ester of the AII antagonist 3b is converted to the hydrazide 13b by the action of hydrazine. In step 2, the hydrazide 13b is first reacted with the symmetrical anhydride of the protected  $\gamma$ -glutamic acid 7 and subsequently reacted with TFA to give the deprotected coupled material 14b. In step 3, the free amino group of 14b is acetylated with acetic anhydride in the presence of base to give the renal-selective angiotensin II antagonist 15b.

The following Examples 1-80 shown in Table IV are angiotensin II antagonists suitable for selection as precursors to provide the first residue of a conjugate of the invention. These angiotensin II antagonists may be prepared generally by the procedures outlined above in Scheme I. Also, specific procedures for preparation of Examples 1-80 of Table IV may be found in EP #253,310 published 20 January 1988.

TABLE IV

Ex. #	$\text{R}^0$	$\text{R}^2$	$\text{R}^1$	$\text{R}^5$
1	$\text{C}_4\text{H}_9$ (n)	$\text{CH}_2\text{OCOCH}_3$	Cl	$\text{CO}_2\text{H}$
2	$\text{C}_4\text{H}_9$ (n)	$\text{CH}_2\text{OH}$	$\text{NO}_2$	$\text{CO}_2\text{H}$
3	$\text{C}_4\text{H}_9$ (n)	$\text{CH}_2\text{OH}$	$\text{CF}_3$	$\text{CO}_2\text{H}$
4	$\text{SC}_3\text{H}_7$	$\text{CH}_2\text{OH}$	H	$\text{CO}_2\text{H}$
5	$\text{C}_4\text{H}_9$ (n)	$\text{CH}_2\text{OH}$	Cl	$\text{CO}_2\text{H}$
6	$\text{C}_4\text{H}_9$ (n)	Cl	$\text{CH}_2\text{OH}$	$\text{CO}_2\text{H}$

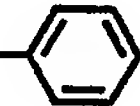



Ex. #	R <sup>0</sup>	R <sup>2</sup>	R <sup>1</sup>	R <sup>5</sup>
7	C <sub>4</sub> H <sub>9</sub> (n)	H	CH <sub>2</sub> OH	CO <sub>2</sub> H
8	C <sub>4</sub> H <sub>9</sub> (n)	CH <sub>2</sub> OH	H	CO <sub>2</sub> H
9	C <sub>4</sub> H <sub>9</sub> (n)	CH <sub>2</sub> OCH <sub>3</sub>	Cl	CO <sub>2</sub> H
10	C <sub>4</sub> H <sub>9</sub> (n)	CH <sub>2</sub> OCH(CH <sub>3</sub> ) <sub>2</sub>	Cl	CO <sub>2</sub> H
11	C <sub>4</sub> H <sub>9</sub> (n)	CH <sub>2</sub> OH	Br	CO <sub>2</sub> H
12	C <sub>4</sub> H <sub>9</sub> (n)	CH <sub>2</sub> OH	F	CO <sub>2</sub> H
13	C <sub>4</sub> H <sub>9</sub> (n)	CH <sub>2</sub> OH	I	CO <sub>2</sub> H
14		CH <sub>2</sub> OH	Cl	CO <sub>2</sub> H
15		CH <sub>2</sub> OH	Cl	CO <sub>2</sub> H
16	C <sub>4</sub> H <sub>9</sub> (n)	I	CH <sub>2</sub> OH	CO <sub>2</sub> H
17	C <sub>3</sub> H <sub>7</sub> (n)	CH <sub>2</sub> OH	Cl	CO <sub>2</sub> H

**SUBSTITUTE SHEET**

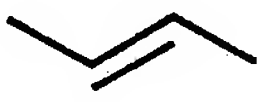
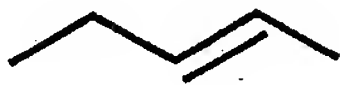
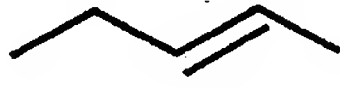
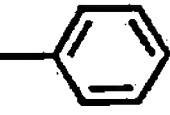
78

Ex. #	R <sup>0</sup>	R <sup>2</sup>	R <sup>1</sup>	R <sup>5</sup>
18	C <sub>2</sub> H <sub>5</sub>	CH <sub>2</sub> OH	Cl	CO <sub>2</sub> H
19	C <sub>3</sub> H <sub>7</sub> (n)	CH <sub>2</sub> OH	Cl	CO <sub>2</sub> H
20	C <sub>5</sub> H <sub>11</sub> (n)	CH <sub>2</sub> OH	Cl	CO <sub>2</sub> H
21	C <sub>6</sub> H <sub>13</sub> (n)	CH <sub>2</sub> OH	Cl	CO <sub>2</sub> H
22	C <sub>4</sub> H <sub>9</sub> (n)	CH <sub>2</sub> SH	Cl	CO <sub>2</sub> H
23	C <sub>4</sub> H <sub>9</sub> (n)	CH <sub>2</sub> OC <sub>6</sub> H <sub>5</sub>	Cl	CO <sub>2</sub> H
24	C <sub>3</sub> H <sub>7</sub> (n)	CHO	Cl	CO <sub>2</sub> H
25	C <sub>4</sub> H <sub>9</sub> (n)	CH <sub>2</sub> CO <sub>2</sub> H	Cl	CO <sub>2</sub> H
26	C <sub>4</sub> H <sub>9</sub> (n)	CH(CH <sub>3</sub> )CO <sub>2</sub> H	Cl	CO <sub>2</sub> H
27	C <sub>4</sub> H <sub>9</sub> (n)	NO <sub>2</sub>	CH <sub>2</sub> OH	CO <sub>2</sub> H
28	C <sub>4</sub> H <sub>9</sub> (n)	CH <sub>2</sub> OCOCH <sub>3</sub>	Cl	CO <sub>2</sub> H

SUBSTITUTE SHEET

Ex. #	R <sup>0</sup>	R <sup>2</sup>	R <sup>1</sup>	R <sup>5</sup>
29	C <sub>4</sub> H <sub>9</sub> (n)	CH <sub>2</sub> OCOCH <sub>2</sub> CH <sub>2</sub> - 	Cl	CO <sub>2</sub> H
30	SC <sub>4</sub> H <sub>9</sub> (n)	CH <sub>2</sub> OH	H	CO <sub>2</sub> H
31	 -CH <sub>2</sub> S	CH <sub>2</sub> OH	H	CO <sub>2</sub> H
32	C <sub>4</sub> H <sub>9</sub> (n)	CHO	Cl	CO <sub>2</sub> H
33	C <sub>4</sub> H <sub>9</sub> (n)	CO <sub>2</sub> CH <sub>3</sub>	Cl	CO <sub>2</sub> H
34	C <sub>4</sub> H <sub>9</sub> (n)	CONH <sub>2</sub>	Cl	CO <sub>2</sub> H
35		CH <sub>2</sub> OH	Cl	CO <sub>2</sub> H
36		CHO	Cl	CO <sub>2</sub> H
37	C <sub>4</sub> H <sub>9</sub> (n)	CHO	H	CO <sub>2</sub> H
38	C <sub>4</sub> H <sub>9</sub> (n)	CHO	CF <sub>3</sub>	CO <sub>2</sub> H
39	C <sub>4</sub> H <sub>9</sub> (n)	CONHCH <sub>3</sub>	Cl	CO <sub>2</sub> H



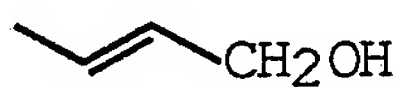
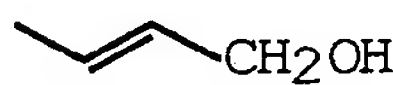
Ex. #	R <sup>0</sup>	R <sup>2</sup>	R <sup>1</sup>	R <sup>5</sup>
40	C <sub>4</sub> H <sub>9</sub> (n)	CON(CH <sub>3</sub> ) <sub>2</sub>	Cl	CO <sub>2</sub> H
41		CH <sub>2</sub> OH	Cl	CO <sub>2</sub> H
42		CH <sub>2</sub> OH	CF <sub>3</sub>	CO <sub>2</sub> H
43		CHO	Cl	CO <sub>2</sub> H
44	C <sub>4</sub> H <sub>9</sub> (n)	$\begin{array}{c} \text{O} \\ \parallel \\ \text{CH}_2\text{-N-C-OC}_2\text{H}_5 \\   \\ \text{H} \end{array}$	Cl	CO <sub>2</sub> H
45	C <sub>4</sub> H <sub>9</sub> (n)	CH <sub>2</sub> NHCO <sub>2</sub> 	Cl	CO <sub>2</sub> H
46	C <sub>4</sub> H <sub>9</sub> (n)	CH <sub>2</sub> NHCO <sub>2</sub> CH <sub>3</sub>	Cl	CO <sub>2</sub> H
47	C <sub>4</sub> H <sub>9</sub> (n)	CH <sub>2</sub> NHCO <sub>2</sub> C <sub>3</sub> H <sub>7</sub>	Cl	CO <sub>2</sub> H
48	C <sub>4</sub> H <sub>9</sub> (n)	CH <sub>2</sub> NHCO <sub>2</sub> CH <sub>2</sub> (CH <sub>3</sub> ) <sub>2</sub>	Cl	CO <sub>2</sub> H

**SUBSTITUTE SHEET**


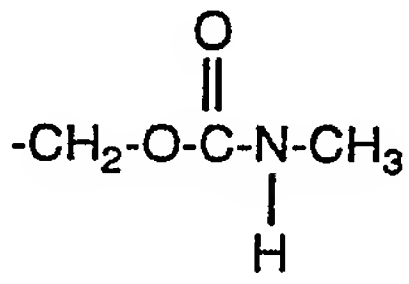
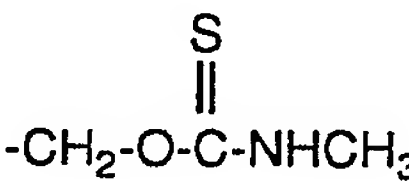
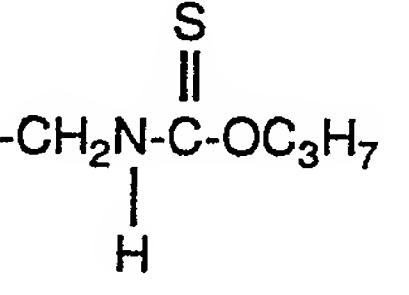
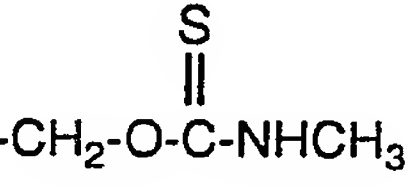
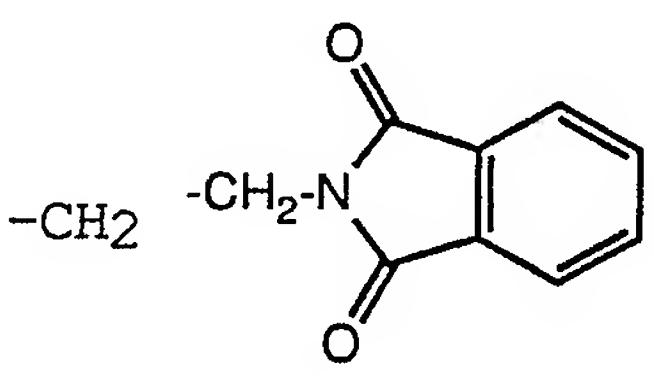
81

Ex. #	R <sup>0</sup>	R <sup>2</sup>	R <sup>1</sup>	R <sup>5</sup>
49	C <sub>4</sub> H <sub>9</sub> (n)	CH <sub>2</sub> NHCO <sub>2</sub> C <sub>4</sub> H <sub>9</sub>	Cl	CO <sub>2</sub> H
50	C <sub>4</sub> H <sub>9</sub> (n)	CH <sub>2</sub> -NHCO <sub>2</sub> -adamantyl	Cl	CO <sub>2</sub> H
51	C <sub>3</sub> H <sub>7</sub> (n)	CH <sub>2</sub> NHCO <sub>2</sub> CH <sub>3</sub>	Cl	CO <sub>2</sub> H
52	C <sub>4</sub> H <sub>9</sub> (n)	CH <sub>2</sub> NHCO <sub>2</sub> CH <sub>3</sub>	Cl	CO <sub>2</sub> H
53	C <sub>4</sub> H <sub>9</sub> (n)	CH <sub>2</sub> NHCO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	Cl	CO <sub>2</sub> H
54	C <sub>4</sub> H <sub>9</sub> (n)	CH <sub>2</sub> NHCO <sub>2</sub> C <sub>3</sub> H <sub>7</sub>	Cl	CO <sub>2</sub> H
55	C <sub>4</sub> H <sub>9</sub> (n)	CH <sub>2</sub> NHCO <sub>2</sub> C <sub>4</sub> H <sub>9</sub>	Cl	CO <sub>2</sub> H
56	C <sub>4</sub> H <sub>9</sub> (n)	CH <sub>2</sub> NHCO <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	Cl	CO <sub>2</sub> H
57	C <sub>4</sub> H <sub>9</sub> (n)	CH <sub>2</sub> NHCO <sub>2</sub> (1-naphthyl)	Cl	CO <sub>2</sub> H
58	C <sub>4</sub> H <sub>9</sub> (n)	CH <sub>2</sub> NHCONHCH <sub>3</sub>	Cl	CO <sub>2</sub> H
59	C <sub>4</sub> H <sub>9</sub> (n)	CH <sub>2</sub> NHCONHC <sub>2</sub> H <sub>5</sub>	Cl	CO <sub>2</sub> H

SUBSTITUTE SHEET

Ex. #	R <sup>0</sup>	R <sup>2</sup>	R <sup>1</sup>	R <sup>5</sup>
60	C <sub>4</sub> H <sub>9</sub> (n)	CH <sub>2</sub> NHCONHC <sub>3</sub> H <sub>7</sub>	Cl	CO <sub>2</sub> H
61	C <sub>4</sub> H <sub>9</sub> (n)	CH <sub>2</sub> NHCONHC <sub>4</sub> H <sub>9</sub>	Cl	CO <sub>2</sub> H
62	C <sub>4</sub> H <sub>9</sub> (n)	CH <sub>2</sub> NHCONHCH(CH <sub>3</sub> ) <sub>2</sub>	Cl	CO <sub>2</sub> H
63	C <sub>4</sub> H <sub>9</sub> (n)	CH <sub>2</sub> NHCONH(1-naphthyl)	Cl	CO <sub>2</sub> H
64	C <sub>3</sub> H <sub>7</sub> (n)	CH <sub>2</sub> CH <sub>2</sub> —C(=O)—N <sub>1,4</sub> -dioxane	H	CO <sub>2</sub> H
65	C <sub>3</sub> H <sub>7</sub> (n)	 CH <sub>2</sub> OH	Cl	CO <sub>2</sub> H
66	C <sub>3</sub> H <sub>7</sub> (n)	 CH <sub>2</sub> OH	Cl	CO <sub>2</sub> H
67	C <sub>4</sub> H <sub>9</sub> (n)	CH <sub>2</sub> CH <sub>2</sub> —C(=O)—N <sub>1,4</sub> -dioxane	Cl	CO <sub>2</sub> H
68	C <sub>4</sub> H <sub>9</sub> (n)	CH <sub>2</sub> CH <sub>2</sub> CO <sub>2</sub> H	Cl	CO <sub>2</sub> H
69	C <sub>4</sub> H <sub>9</sub> (n)	CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CO <sub>2</sub> H	Cl	CO <sub>2</sub> H

83

Ex. #	R <sup>0</sup>	R <sup>2</sup>	R <sup>1</sup>	R <sup>5</sup>
70		CH <sub>2</sub> OH	Cl	CO <sub>2</sub> H
71	C <sub>4</sub> H <sub>9</sub> (n)		Cl	CO <sub>2</sub> H
72	C <sub>4</sub> H <sub>9</sub> (n)		Cl	CO <sub>2</sub> H
73	C <sub>4</sub> H <sub>9</sub> (n)		H	CO <sub>2</sub> H
74	C <sub>4</sub> H <sub>9</sub> (n)		H	CO <sub>2</sub> H
75	C <sub>4</sub> H <sub>9</sub> (n)	-CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> F	Cl	CO <sub>2</sub> H
76	C <sub>4</sub> H <sub>9</sub> (n)	-CH <sub>2</sub> ONO <sub>2</sub>	Cl	CO <sub>2</sub> H
77	C <sub>4</sub> H <sub>9</sub> (n)		Cl	CO <sub>2</sub> H

SUBSTITUTE SHEET

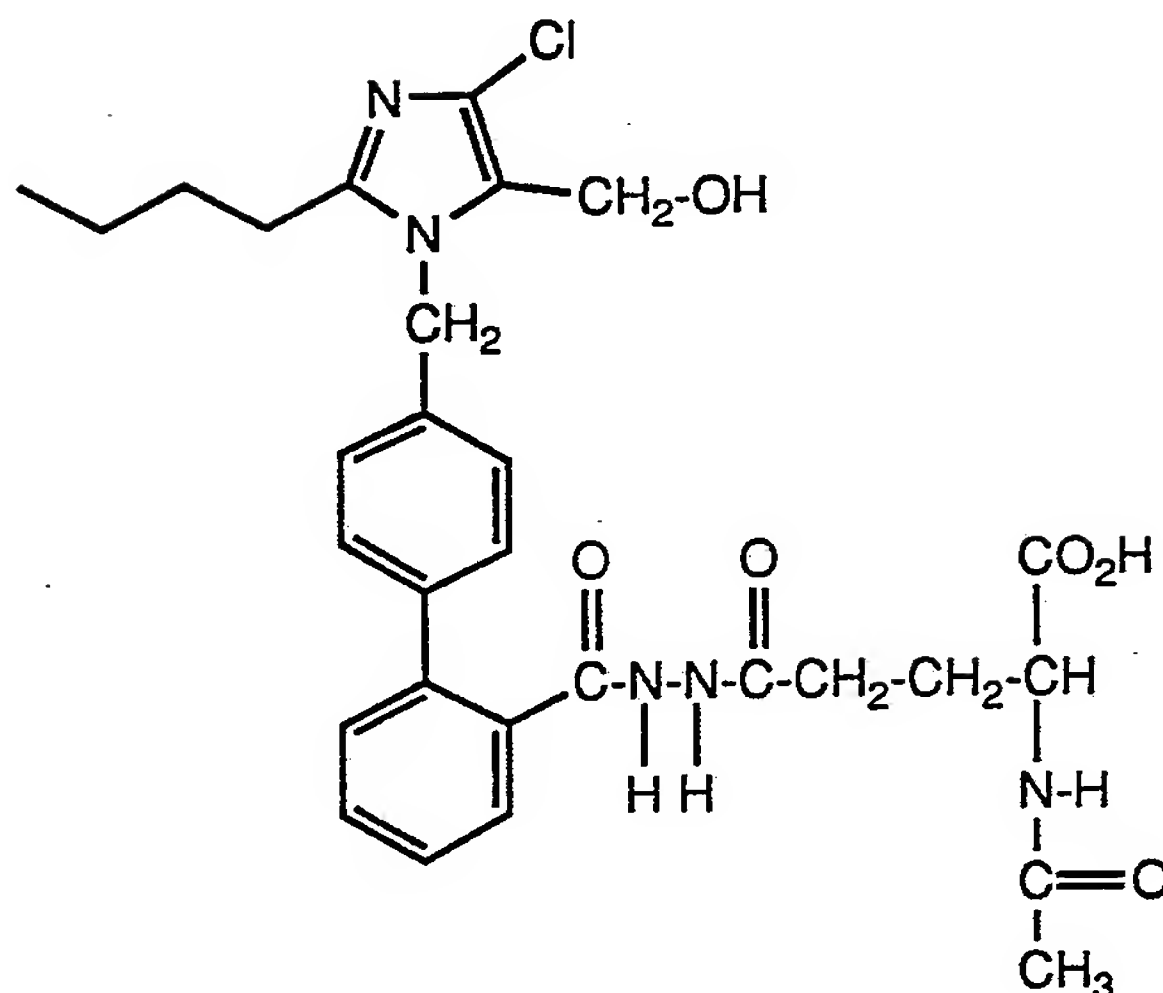
84

Ex. #	R <sup>0</sup>	R <sup>2</sup>	R <sup>1</sup>	R <sup>5</sup>
78	C <sub>4</sub> H <sub>9</sub> (n)	CH <sub>2</sub> OH	Cl	CN <sub>4</sub> H
79	C <sub>4</sub> H <sub>9</sub> (n)	Cl	CH <sub>2</sub> OH	CN <sub>4</sub> H
80	C <sub>4</sub> H <sub>9</sub> (n)	CHO	Cl	CN <sub>4</sub> H

SUBSTITUTE SHEET

A class of highly preferred specific conjugates of the invention is provided by conjugates formed from a biphenylmethyl 1H-substituted imidazole AII antagonist compound linked to a cleavable glutamyl residue. Each conjugate contains a diamino linker moiety which connects a terminal carboxylic acid moiety on the biphenylmethyl portion of the AII antagonist compound with a terminal carboxylic acid moiety on the gamma carbon of the cleavable glutamyl residue. Such conjugates are shown herein as Examples 81-146. General procedures for preparation of the conjugates of Examples 81-146 are described in Schemes II-III. Detailed procedures for preparation of representative conjugates are described in Examples 81 and 82. Similar procedures may be used for preparation of the conjugates identified as Examples 83-146 shown in Table V.

## Example 81



5 N-acetyl-L-glutamic acid, 5-[[[4'-[2-butyl-4-chloro-5-(hydroxymethyl)-1H-imidazol-1-ylmethyl][1,1'-biphenyl]-2-yl]carbonyl]hydrazide

10 Step 1: Preparation of 1-[(2'-methoxycarbonyl-biphenyl-4-yl)methyl]-2-butyl-4-chloro-5-hydroxymethylimidazole.

Under nitrogen, a solution of 6.69 g (36 mmol) of 2-butyl-4-chloro-5-hydroxymethylimidazole in 100 mL of anhydrous dimethylformamide (DMF) was treated with molecular sieves and 11.0 g (36 mmol) of 4-bromomethyl-2'-methoxycarbonylbiphenyl. The reaction was allowed to stir at ambient temperature overnight and then was filtered. The DMF was removed in vacuo and the residue was partitioned between water and chloroform; the chloroform extracts were combined, dried (MgSO<sub>4</sub>), and concentrated in vacuo giving 17.4 g of



crude material. Purification by silica gel chromatography (Waters Prep-500A) using ethyl acetate/hexane (40:60) gave the 4-hydroxymethyl isomer as the regioisomer with the lower  $R_f$  value and 6.27 g (42%) of the 5-hydroxymethyl isomer: NMR (CDCl<sub>3</sub>)  $\delta$  0.91 (t,  $J=7$ Hz, 3H), 1.29-1.44 (m, 2H), 1.52 (t,  $J=8$ Hz, 1H), 1.63-1.76 (m, 2H), 2.62 (t,  $J=7$ Hz, 2H), 3.65 (s, 3H), 4.54 (d,  $J=8$ Hz, 2H), 7.02-7.08 (m, 2H), 7.25-7.36 (m, 3H), 7.38-7.47 (m, 1H), 7.50-7.58 (m, 1H), 7.83-7.90 (m, 1H).

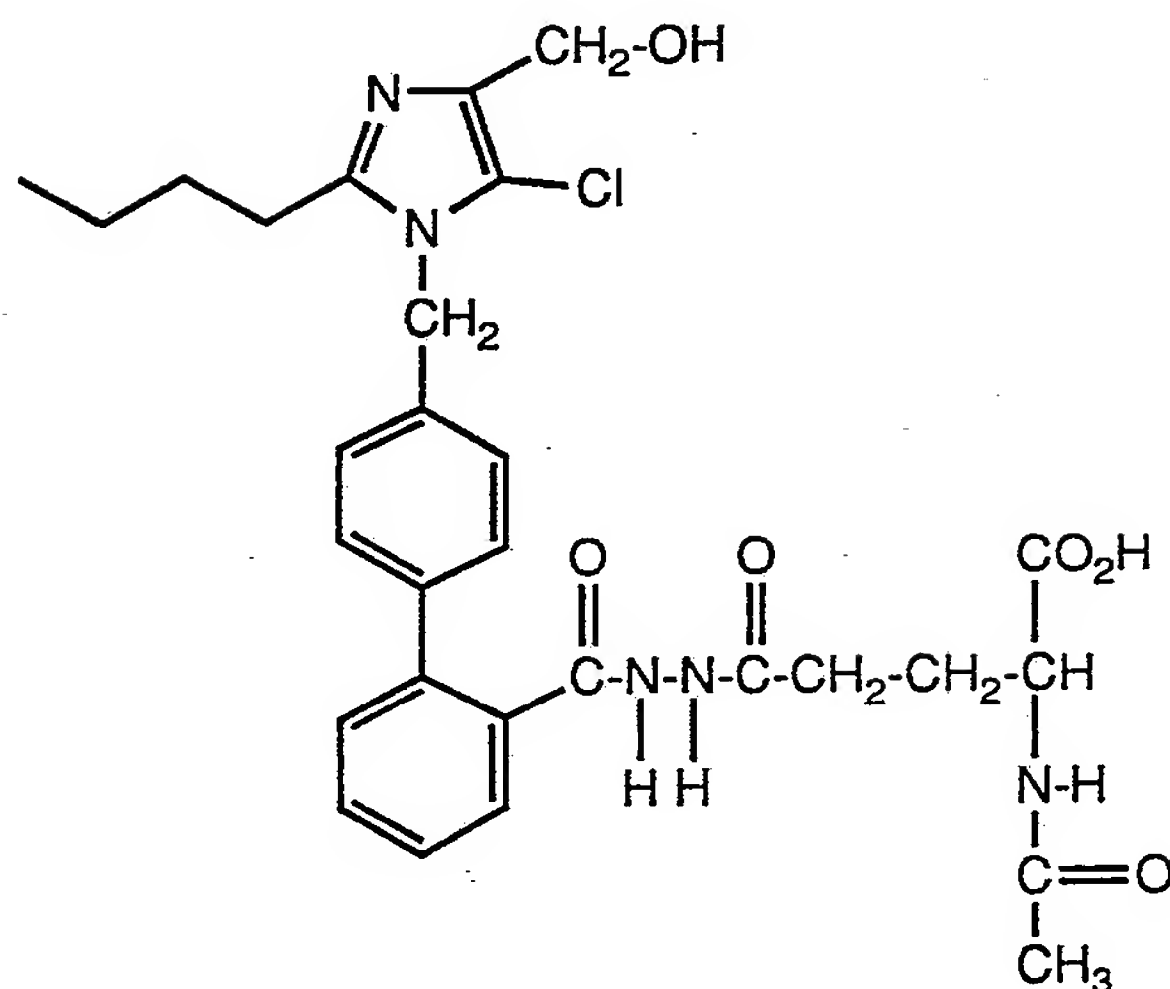
Step 2: Preparation of 1-[(2'-hydrazinylcarbonyl-biphenyl-4-yl)methyl]-2-butyl-4-chloro-5-hydroxymethylimidazole.

Under nitrogen, 6.27 g (15 mmol) of the 5-hydroxymethyl ester from step 1 was dissolved in 100 mL of methanol and treated with 15 mL (480 mmol) of anhydrous hydrazine. The reaction was allowed to stir at reflux overnight; concentration in vacuo gave 4.83 g of crude material. Purification by silica gel chromatography (Waters Prep-500A) using isopropanol/ethyl acetate (20:80) gave 4.27 g (68%) of the hydrazide as a colorless glass: NMR (CDCl<sub>3</sub>)  $\delta$  0.81 (t,  $J=7$ Hz, 3H), 1.18-1.34 (m, 2H), 1.42-1.56 (m, 2H), 2.50 (t,  $J=$ Hz, 2H), 4.15-4.35 (br s, 2H), 4.35 (d,  $J=8$ Hz, 2H), 5.24 (t,  $J=8$ Hz, 1H), 7.05-7.13 (m, 2H), 7.32-7.44 (m, 5H), 7.45-7.54 (m, 1H), 9.34 (s, 1H).

Step 3: Preparation of N-acetyl-L-glutamic acid, 5-[[4'-(2-butyl-4-chloro-5-(hydroxymethyl)-1H-imidazol-1-yl)methyl][1,1'-biphenyl]-2-yl]carbonylhydrazide.

5                   To a solution of 1.70 g (5.60 mmol) of N-Boc-L-glutamic acid- $\alpha$ -tertbutyl ester (BACHEM) in 50 mL of methylene chloride under nitrogen was added 580 mg (2.8 mmol) of solid dicyclohexylcarbodiimide (DCC). The reaction was allowed to stir for 2 h and filtered under nitrogen. The anhydride  
10 solution was then added to a solution of 1.0 g (2.4 mmol) of hydrazide from step 2 in 75 mL of methylene chloride under nitrogen. The reaction was stirred overnight, concentrated to a volume of 25 mL, cooled to 0°C, and treated with 25 mL of TFA under nitrogen. The stirred reaction was allowed to warm  
15 to ambient temperature overnight and concentrated in vacuo. The crude product was dissolved in 100 mL of acetonitrile/water (1:1) and the pH adjusted to 8 with 1 M K<sub>2</sub>CO<sub>3</sub>. The solution was cooled to 0°C and 0.23 mL (2.4 mmol) of acetic anhydride and 2.4 mL (2.4 mmol) of 1 M K<sub>2</sub>CO<sub>3</sub> was  
20 added every 30 min for 5 h; the pH was maintained at 9 and the reaction temperature kept below 5°C. After the last addition, the reaction was allowed to warm to ambient temperature overnight. The pH was adjusted to 4 with 3 M HCl and the reaction was concentrated to 100 mL. Purification by reverse  
25 phase chromatography (Waters Deltaprep-3000) using isocratic 25% acetonitrile/water (0.05% TFA) gave 1.0 g (75% overall yield from the hydrazide of step 2) of colorless product: NMR (DMSO-d<sub>6</sub>)  $\delta$  0.81 (t,  $J$ =7Hz, 3H), 1.20-1.30 (m, 2H), 1.42-1.55 (m, 2H), 1.75-1.84 (m, 2H), 1.85 (s, 3H), 1.89-2.05 (m, 2H),  
30 2.21 (t,  $J$ =7Hz, 2H), 4.13-4.24 (m, 1H), 4.35 (s, 2H), 7.05-7.12 (m, 2H), 7.37-7.58 (m, 6H), 8.12-8.17 (m, 2H); MS (FAB) m/e (rel. intensity) 584 (18), 568 (100), 225 (64); HRMS. Calcd for M+H: 584.2276. Found: 584.2240.

## Example 82



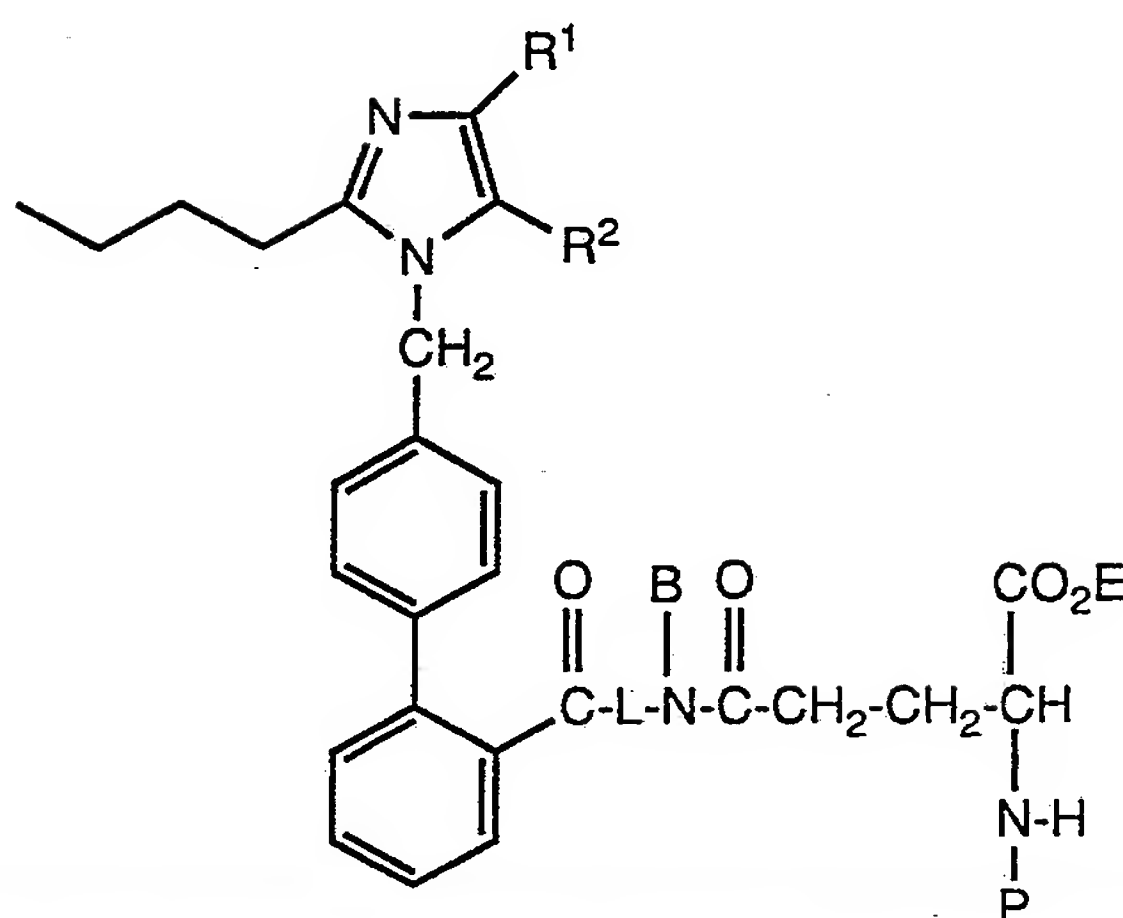
5 N-acetyl-L-glutamic acid, 5-[[4'-[2-butyl-5-chloro-4-(hydroxymethyl)-1H-imidazol-1-ylmethyl][1,1'-biphenyl]-2-yl]carbonyl]hydrazide

Step 1: Preparation of 1-[(2'-hydrazinylcarbonyl-biphenyl-4-yl)methyl]-2-butyl-5-chloro-4-hydroxymethylimidazole.

10 Under nitrogen, 4.13 g (10 mmol) of the 4-hydroxymethyl ester from step 1 of Example 81 is dissolved in 100 mL of methanol and is treated with 15 mL of (480 mmol) of anhydrous hydrazine. The reaction is allowed to stir at reflux overnight; concentration in vacuo gives the crude material. Purification by silica gel chromatography (Waters  
15 Prep-500A) gives the pure hydrazide.

Step 2: Preparation of N-acetyl-L-glutamic acid, 5-[[4'-(2-butyl-5-chloro-4-(hydroxymethyl)-1H-imidazol-1-yl)methyl][1,1'-biphenyl]-2-yl]carbonyl]hydrazide

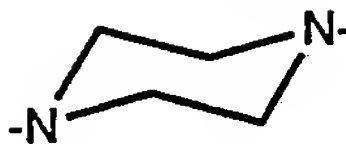
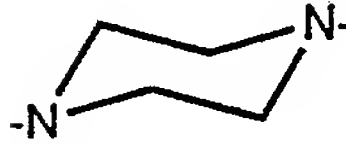
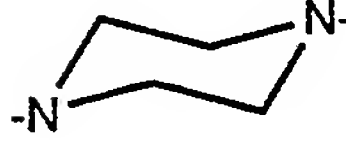
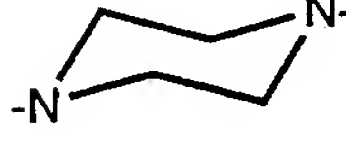
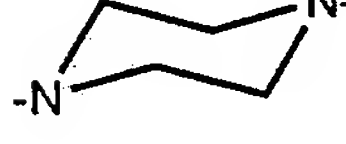

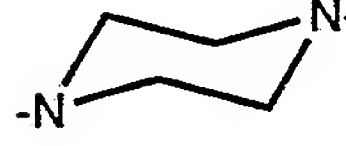

5                   To a solution of 1.70 g (5.6 mmol) of N-Boc-L-glutamic acid- $\alpha$ -tertbutyl ester (BACHEM) in 50 mL of methylene chloride under nitrogen is added 580 mg (2.8 mmol) of solid dicyclohexylcarbodiimide (DCC). The reaction is allowed to stir for 2 h and is filtered under nitrogen. The anhydride  
10 solution is then added to a solution of 1.0 g (2.4 mmol) of the hydrazide from step 1 in 75 mL of methylene chloride under nitrogen. The reaction is stirred overnight, is concentrated to a volume of 25 mL, is cooled to 0°C, and is treated with 25 mL of TFA under nitrogen. The stirred reaction is allowed  
15 to warm to ambient temperature overnight and is concentrated in vacuo. The crude product is dissolved in 100 mL of acetonitrile/water (1:1) and the pH is adjusted to 8 with 1 M K<sub>2</sub>CO<sub>3</sub>. The solution is cooled to 0°C and 0.23 mL (2.4 mmol) of acetic anhydride and 2.4 mL (2.4 mmol) of 1 M K<sub>2</sub>CO<sub>3</sub> is  
20 added every 30 min for 5 h; the pH is maintained at 9 and the reaction temperature is kept below 5°C. After the last addition, the reaction is allowed to warm to ambient temperature overnight. The pH is adjusted to 4 with 3 M HCl and the reaction is concentrated to 100 mL. Purification by  
25 reverse phase chromatography (Waters Deltaprep-3000) gives the product.

TABLE V

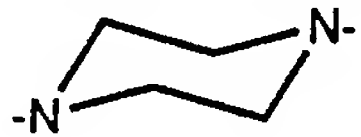
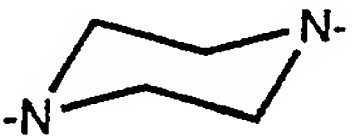
Ex. #	R <sup>2</sup>	R <sup>1</sup>	L	B	E	P
83	CH <sub>2</sub> OH	Cl	-NH-	H	H	H
84	CH <sub>2</sub> OH	Cl	-NH-	H	CH <sub>3</sub>	H
85	CH <sub>2</sub> OH	Cl	-NH-	H	CH <sub>3</sub>	COCH <sub>3</sub>
86	CH <sub>2</sub> OH	Cl	-NH-	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
87	CH <sub>2</sub> OH	Cl	-NH-	H	C <sub>2</sub> H <sub>5</sub>	H
88	CH <sub>2</sub> OH	Cl	-NH-	H	H	COCH <sub>2</sub> Cl
89	CH <sub>2</sub> OH	Cl	-NH-	H	H	COC <sub>4</sub> H <sub>9</sub> (n)

Ex. #	R <sup>2</sup>	R <sup>1</sup>	L	B	E	P
90	Cl	CH <sub>2</sub> OH	-NH-	H	H	H
91	CH <sub>2</sub> OH	Cl	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>3</sub>
92	CH <sub>2</sub> OH	Cl	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	H
93	CH <sub>2</sub> OH	Cl	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	CH <sub>3</sub>	H
94	CH <sub>2</sub> OH	Cl	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	CH <sub>3</sub>	COCH <sub>3</sub>
95	CH <sub>2</sub> OH	Cl	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
96	CH <sub>2</sub> OH	Cl	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	C <sub>2</sub> H <sub>5</sub>	H
97	CH <sub>2</sub> OH	Cl	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>2</sub> Cl
98	CH <sub>2</sub> OH	Cl	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COC <sub>4</sub> H <sub>9</sub> (n)
99	Cl	CH <sub>2</sub> OH	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>3</sub>
100	Cl	CH <sub>2</sub> OH	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	H



Ex. #	R <sup>2</sup>	R <sup>1</sup>	L	B	E	P
101	CH <sub>2</sub> OH	Cl		*	H	COCH <sub>3</sub>
102	CH <sub>2</sub> OH	Cl		*	H	H
103	CH <sub>2</sub> OH	Cl		*	CH <sub>3</sub>	H
104	CH <sub>2</sub> OH	Cl		*	CH <sub>3</sub>	COCH <sub>3</sub>
105	CH <sub>2</sub> OH	Cl		*	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
106	CH <sub>2</sub> OH	Cl		*	C <sub>2</sub> H <sub>5</sub>	H
107	CH <sub>2</sub> OH	Cl		*	H	COC <sub>4</sub> H <sub>9</sub> (n) )
108	CH <sub>2</sub> OH	Cl		*	H	COC <sub>4</sub> H <sub>9</sub> (n) )

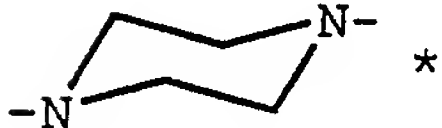

SUBSTITUTE SHEET

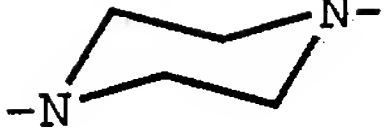
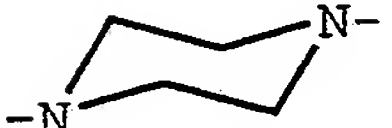
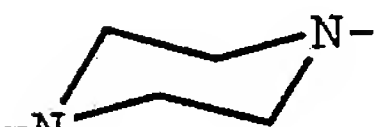
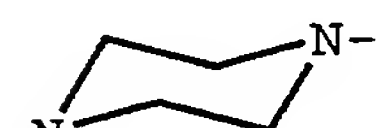

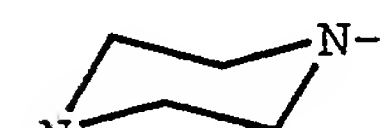
Ex. #	R <sup>2</sup>	R <sup>1</sup>	L	B	E	P
109	Cl	CH <sub>2</sub> OH		*	H	COCH <sub>3</sub>
110	Cl	CH <sub>2</sub> OH		*	H	H
111	CH <sub>2</sub> OCH <sub>3</sub>	Cl	-NH-	H	H	COCH <sub>3</sub>
112	CH <sub>2</sub> OCH <sub>3</sub>	Cl	-NH-	H	H	H
113	Cl	CH <sub>2</sub> OCH <sub>3</sub>	-NH-	H	H	COCH <sub>3</sub>
114	Cl	CH <sub>2</sub> OCH <sub>3</sub>	-NH-	H	H	H
115	CH <sub>2</sub> OH	CF <sub>3</sub>	-NH-	H	H	COCH <sub>3</sub>
116	CH <sub>2</sub> OH	CF <sub>3</sub>	-NH-	H	H	H
117	CH <sub>2</sub> OH	C <sub>2</sub> F <sub>5</sub>	-NH-	H	H	COCH <sub>3</sub>
118	CH <sub>2</sub> OH	C <sub>2</sub> F <sub>5</sub>	-NH-	H	H	H
119	CH <sub>2</sub> OH	C <sub>3</sub> F <sub>7</sub>	-NH-	H	H	COCH <sub>3</sub>


SUBSTITUTE SHEET

Ex. #	R <sup>2</sup>	R <sup>1</sup>	L	B	E	P
120	CH <sub>2</sub> OH	C <sub>3</sub> F <sub>7</sub>	-NH-	H	H	H
121	CHO	Cl	-NH-	H	H	COCH <sub>3</sub>
122	CHO	Cl	-NH-	H	H	H
123	Cl	CHO	-NH-	H	H	COCH <sub>3</sub>
124	Cl	CHO	-NH-	H	H	H
125	CO <sub>2</sub> H	Cl	-NH-	H	H	COCH <sub>3</sub>
126	CO <sub>2</sub> H	Cl	-NH-	H	H	COCH <sub>3</sub>
127	Cl	CO <sub>2</sub> H	-NH-	H	H	COCH <sub>3</sub>
128	Cl	CO <sub>2</sub> H	-NH-	H	H	H
129	CH <sub>2</sub> OH	Br	-NH-	H	H	COCH <sub>3</sub>
130	CH <sub>2</sub> OH	Br	-NH-	H	H	H

SUBSTITUTE SHEET

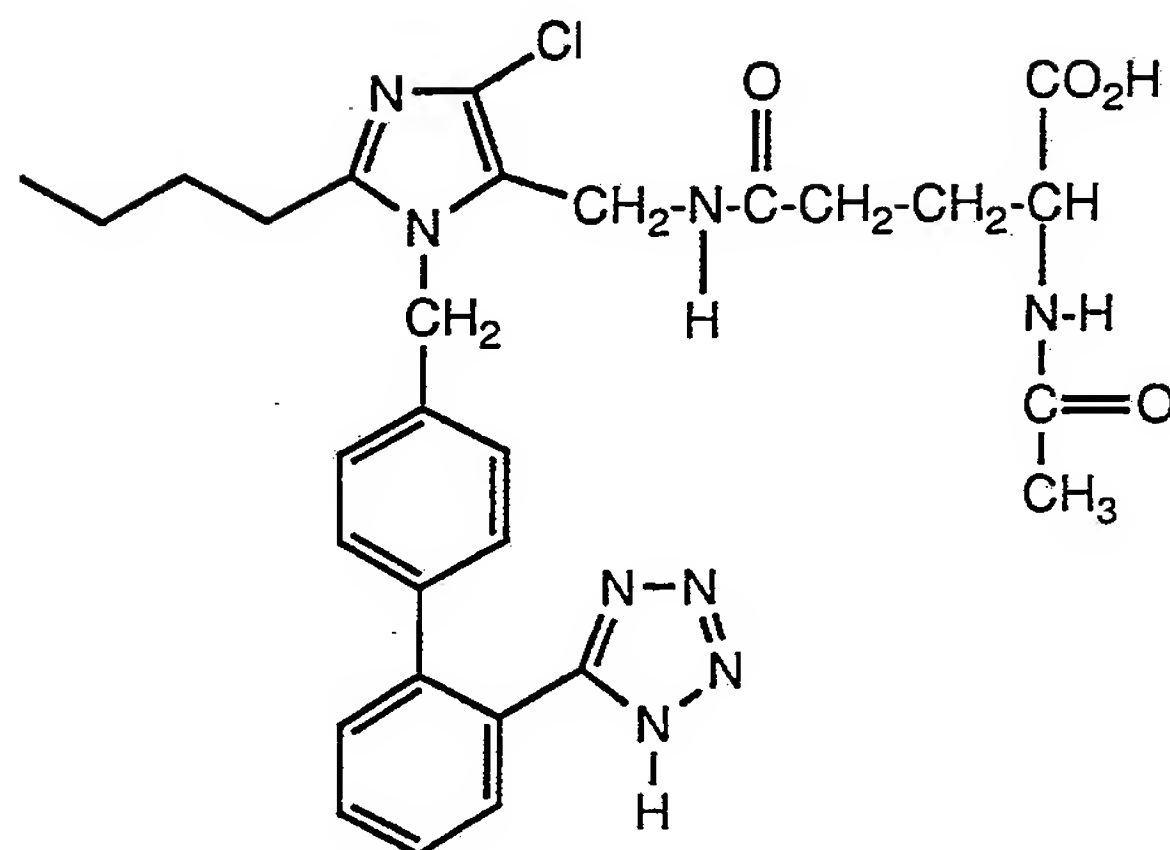
Ex. #	R <sup>2</sup>	R <sup>1</sup>	L	B	E	P
131	Cl	CHO	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>3</sub>
132	Cl	CHO	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	H
133	CO <sub>2</sub> H	Cl	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>3</sub>
134	CO <sub>2</sub> H	Cl	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	H
135	Cl	CO <sub>2</sub> H	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>3</sub>
136	Cl	CO <sub>2</sub> H	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	H
137	CH <sub>2</sub> OH	Br	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>3</sub>
138	CH <sub>2</sub> OH	Br	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	H
139	Cl	CHO		H	H	COCH <sub>3</sub>
140	Cl	CHO		H	H	H

Ex. #	R <sup>2</sup>	R <sup>1</sup>	L	B	E	P
141	CO <sub>2</sub> H	Cl		*	H	COCH <sub>3</sub>
142	CO <sub>2</sub> H	Cl		*	H	H
143	Cl	CO <sub>2</sub> H		*	H	COCH <sub>3</sub>
144	Cl	CO <sub>2</sub> H		*	H	H
145	CH <sub>2</sub> OH	Br		*	H	COCH <sub>3</sub>
146	CH <sub>2</sub> OH	Br		*	H	H

\*  equals piperazinyl

Another class of highly preferred specific conjugates of the invention is provided by conjugates formed from a biphenylmethyl 1H-substituted imidazole AII antagonist compound having a terminal amino group attached to the imidazole nucleus. In this family of conjugates, the cleavable glutamyl residue is attached through an amide bond formed between the carbonyl at the gamma carbon of the glutamyl residue and the terminal amino nitrogen of the AII antagonist imidazole nucleus. Such conjugates are shown as Examples #147-#710. General procedures for preparation of the conjugates of Examples #147-#710 are described in Schemes IV-V. Detailed procedures for preparation of representative conjugates are described in Examples #147 and #148. Procedures similar to these aforementioned general and specific procedures may be used for preparation of the conjugates identified as Examples #149-#710 shown in Table VI.

## Example 147



5 N2-acetyl-N-[[2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazol-5-yl]methyl]-L-glutamine

Step 1: Preparation of 5-aminomethyl-2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)biphenyl]-4-methyl]imidazole.

- 10 A solution of 4.20 g (10 mmol) of the compound of Example 80, 7.7 g (100 mmol) of ammonium acetate, and 439 mg (7 mmol) of NaBH<sub>3</sub>CN in 30 mL of absolute methanol is stirred at ambient temperature for 48 h. Concentrated HCl is added until pH<2, and the methanol is removed in vacuo.
- 15 The residue is dissolved in water and is extracted with ethyl acetate. The aqueous solution is brought to pH>10 with 50% NaOH, is saturated with NaCl, and is extracted with methylene chloride. The extracts are combined, are dried (MgSO<sub>4</sub>), and are evaporated in vacuo to give the
- 20 crude product. Purification by reverse phase chromatography (Waters DeltaPrep-3000) provides the pure 5-aminomethyl product.

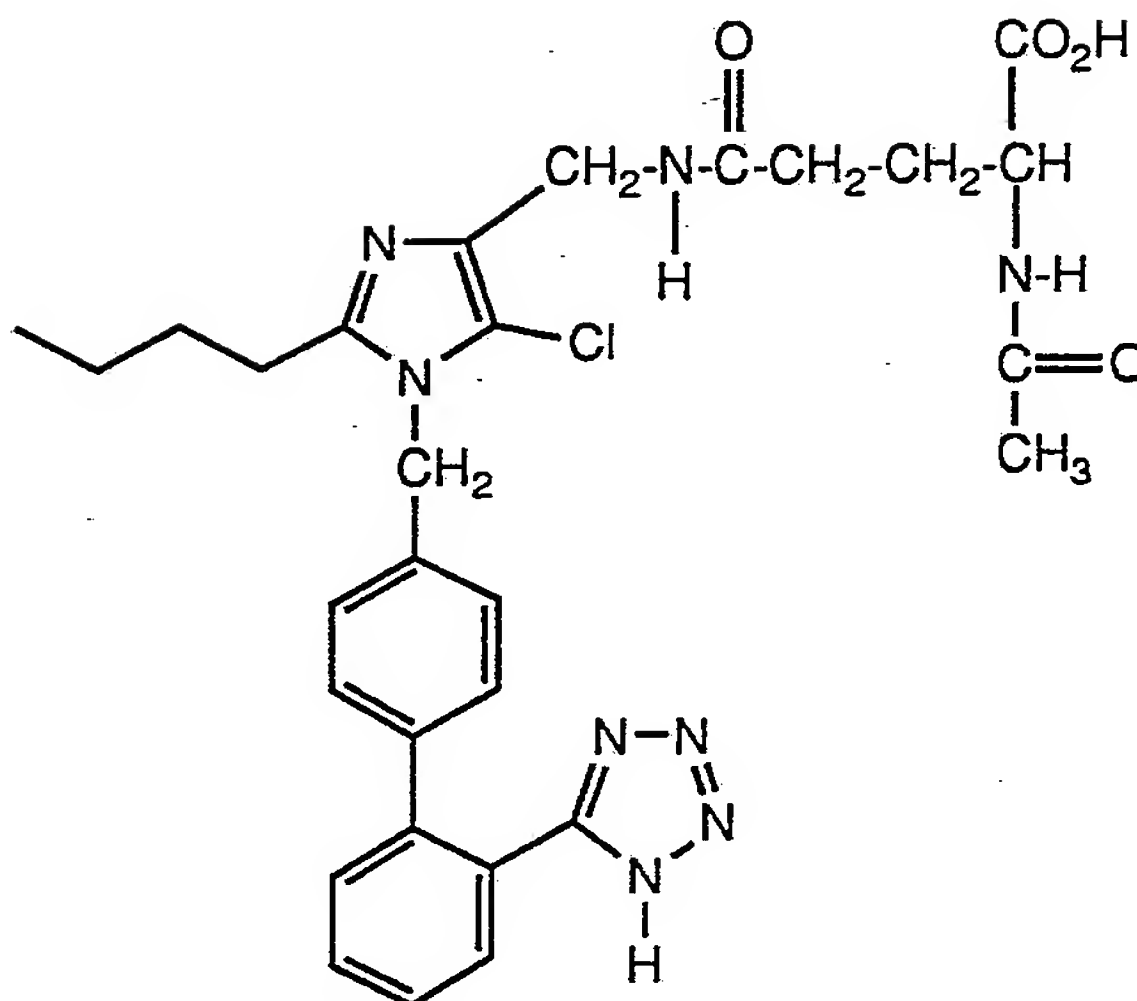


Step 2: Preparation of N2-acetyl-N-[[2-butyl-4-chloro-1-  
[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-  
imidazol-5-yl]methyl]-L-glutamine

5

To a solution of 1.70 g (5.6 mmol) of N-Boc-L-glutamic acid- $\alpha$ -tertbutyl ester (BACHEM) in 50 mL of methylene chloride under nitrogen is added 580 mg (2.8 mmol) of solid dicyclohexylcarbodiimide (DCC). The  
10 reaction is allowed to stir for 2 h and is filtered under nitrogen. The anhydride solution is then added to a solution of 1.01 g (2.4 mmol) of the 5-aminomethyl compound of step 1 in 75 mL of methylene chloride under nitrogen. The reaction is stirred overnight, is concentrated to a  
15 volume of 25 mL, is cooled to 0°C, and is treated with 25 mL of TFA under nitrogen. The stirred reaction is allowed to warm to ambient temperature overnight and is concentrated in vacuo. The crude product is dissolved in 100 mL of acetonitrile/water (1:1) and the pH is adjusted  
20 to 8 with 1 M K<sub>2</sub>CO<sub>3</sub>. The solution is cooled to 0°C and 0.23 mL (2.4 mmol) of acetic anhydride and 2.4 mL (2.4 mmol) of 1 M K<sub>2</sub>CO<sub>3</sub> is added every 30 min for 5 h; the pH is maintained at 9 and the reaction temperature is kept below 5°C. After the last addition, the reaction is allowed to  
25 warm to ambient temperature overnight. The pH is adjusted to 4 with 3 M HCl and the reaction is concentrated to 100 mL. Purification by reverse phase chromatography (Waters Delta- prep-3000) gives the pure product.

## Example 148



5 N2-acetyl-N-[[2-butyl-5-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazol-4-yl]methyl]-L-glutamine

Step 1: Preparation of 2-butyl-5-chloro-4-formyl-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-methyl]imidazole.

10 A mixture of 2.11 g (5.0 mmol) of the compound of Example 79 and 3.08 g (35 mmol) of activated manganese dioxide in 30 mL of methylene chloride at ambient temperature is stirred for 40 h. The reaction mixture is filtered through celite, and the filtrate is concentrated  
15 in vacuo. Purification by reverse phase chromatography provided the pure 4-formyl product.

Step 2: Preparation of 4-aminomethyl-2-butyl-5-chloro-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-methyl]imidazole.

20

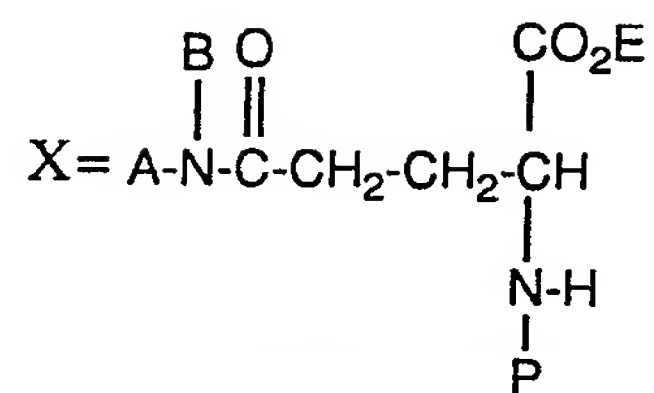
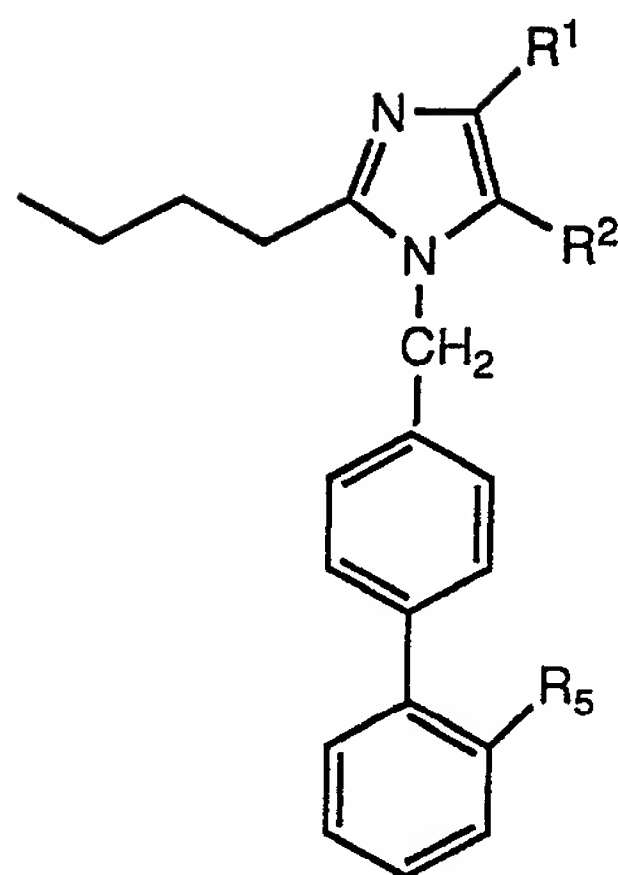
A solution of 4.20 g (10 mmol) of the aldehyde from step 1, 7.7 g (100 mmol) of ammonium acetate, and 439

mg (7 mmol) of NaBH<sub>3</sub>CN in 30 mL of absolute methanol is stirred at ambient temperature for 48 h. Concentrated HCl is added until pH<2, and the methanol is removed in vacuo. The residue is dissolved in water and is extracted with ethyl acetate. The aqueous solution is brought to pH>10 with 50% NaOH, is saturated with NaCl, and is extracted with methylene chloride. The extracts are combined, are dried (MgSO<sub>4</sub>), and are evaporated in vacuo to give the crude product. Purification by reverse phase chromatography (Waters Deltaprep-3000) provides the pure product.

Step 3: Preparation of N2-acetyl-N-[[2-butyl-5-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazol-4-yl]methyl]-L-glutamine

To a solution of 1.70 g (5.6 mmol) of N-Boc-L-glutamic acid- $\alpha$ -tertbutyl ester (BACHEM) in 50 mL of methylene chloride under nitrogen is added 580 mg (2.8 mmol) of solid dicyclohexylcarbodiimide (DCC). The reaction is allowed to stir for 2 h and is filtered under nitrogen. The anhydride solution is then added to a solution of 1.01 g (2.4 mmol) of the 4-aminomethyl compound of step 2 in 75 mL of methylene chloride under nitrogen. The reaction is stirred overnight, is concentrated to a volume of 25 mL, is cooled to 0°C, and is treated with 25 mL of TFA under nitrogen. The stirred reaction is allowed to warm to ambient temperature overnight and is concentrated in vacuo. The crude product is dissolved in 100 mL of acetonitrile/water (1:1) and the pH is adjusted to 8 with 1 M K<sub>2</sub>CO<sub>3</sub>. The solution is cooled to 0°C and 0.23 mL (2.4 mmol) of acetic anhydride and 2.4 mL (2.4 mmol) of 1 M K<sub>2</sub>CO<sub>3</sub> is added every 30 min for 5 h; the pH is maintained at 9 and the reaction temperature is kept below

5°C. After the last addition, the reaction is allowed to warm to ambient temperature overnight. The pH is adjusted to 4 with 3 M HCl and the reaction is concentrated to 100 mL. Purification by reverse phase chromatography (Waters 5 Delta-prep-3000) gives the pure product.

**TABLE VI**

Ex: #	R <sup>1</sup>	R <sup>2</sup>	R <sub>5</sub>	A	B	E	P
149	Cl	X	CO <sub>2</sub> H	single bond	H	H	COCH <sub>3</sub>
150	Cl	X	CO <sub>2</sub> H	single bond	H	H	COCH <sub>2</sub> Cl
151	Cl	X	CO <sub>2</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>
152	Cl	X	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>
153	Cl	X	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
154	Cl	X	CN <sub>4</sub> H	single bond	H	H	COCH <sub>3</sub>

Ex: #	R <sup>1</sup>	R <sup>2</sup>	R <sub>5</sub>	A	B	E	P
155	Cl	X	CN <sub>4</sub> H	single bond	H	H	COCH <sub>2</sub> Cl
156	Cl	X	CN <sub>4</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>
157	Cl	X	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>
158	Cl	X	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
159	Cl	X	CO <sub>2</sub> H	single bond	H	H	H
160	Cl	X	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	H
161	Cl	X	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
162	Cl	X	CN <sub>4</sub> H	single bond	H	H	H
163	Cl	X	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	H
164	Cl	X	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
165	Cl	X	CO <sub>2</sub> H	-CH <sub>2</sub> -	H	H	COCH <sub>3</sub>
166	Cl	X	CO <sub>2</sub> H	single bond	H	H	COCH <sub>2</sub> Cl

**SUBSTITUTE SHEET**

Ex: #	R <sup>1</sup>	R <sup>2</sup>	R <sub>5</sub>	A	B	E	P
167	Cl	X	CO <sub>2</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>
168	Cl	X	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>
169	Cl	X	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
170	Cl	X	CN <sub>4</sub> H	single bond	H	H	COCH <sub>2</sub> Cl
171	Cl	X	CN <sub>4</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>
172	Cl	X	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>
173	Cl	X	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
174	Cl	X	CO <sub>2</sub> H	-CH <sub>2</sub> -	H	H	H
175	Cl	X	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	H
176	Cl	X	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
177	Cl	X	CN <sub>4</sub> H	-CH <sub>2</sub> -	H	H	H

SUBSTITUTE SHEET

Ex: #	R <sup>1</sup>	R <sup>2</sup>	R <sub>5</sub>	A	B	E	P
178	Cl	X	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	H
179	Cl	X	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
180	Cl	X	CN <sub>4</sub> H	-CH <sub>2</sub> -	CH <sub>3</sub>	H	H
181	Cl	X	CN <sub>4</sub> H	-CH <sub>2</sub> -	CH <sub>3</sub>	H	COCH <sub>3</sub>
182	Cl	X	CO <sub>2</sub> H	-CH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>3</sub>
183	Cl	X	CO <sub>2</sub> H	single bond	H	H	COCH <sub>2</sub> Cl
184	Cl	X	CO <sub>2</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>
185	Cl	X	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>
186	Cl	X	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
187	Cl	X	CN <sub>4</sub> H	-CH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>3</sub>
188	Cl	X	CN <sub>4</sub> H	single bond	H	H	COCH <sub>2</sub> Cl

SUBSTITUTE SHEET



Ex: #	R <sup>1</sup>	R <sup>2</sup>	R <sub>5</sub>	A	B	E	P
189	Cl	X	CN <sub>4</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>
190	Cl	X	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>
191	Cl	X	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
192	Cl	X	CO <sub>2</sub> H	-CH <sub>2</sub> CH <sub>2</sub> -	H	H	H
193	Cl	X	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	H
194	Cl	X	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
195	Cl	X	CN <sub>4</sub> H	-CH <sub>2</sub> CH <sub>2</sub> -	H	H	H
196	Cl	X	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	H
197	Cl	X	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
198	Cl	X	CO <sub>2</sub> H	C <sub>3</sub> H <sub>6</sub> (n)	H	H	COCH <sub>3</sub>
199	Cl	X	CO <sub>2</sub> H	single bond	H	H	COCH <sub>2</sub> Cl

SUBSTITUTE SHEET


Ex: #	R <sup>1</sup>	R <sup>2</sup>	R <sub>5</sub>	A	B	E	P
200	Cl	X	CO <sub>2</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>
201	Cl	X	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>
202	Cl	X	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
203	Cl	X	CN <sub>4</sub> H	C <sub>3</sub> H <sub>6</sub> (n)	H	H	COCH <sub>3</sub>
204	Cl	X	CN <sub>4</sub> H	single bond	H	H	COCH <sub>2</sub> Cl
205	Cl	X	CN <sub>4</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>
206	Cl	X	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>
207	Cl	X	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
208	Cl	X	CO <sub>2</sub> H	C <sub>3</sub> H <sub>6</sub> (n)	H	H	H
209	Cl	X	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	H
210	Cl	X	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H

**SUBSTITUTE SHEET**




111

Ex: #	R <sup>1</sup>	R <sup>2</sup>	R <sub>5</sub>	A	B	E	P
211	Cl	X	CN <sub>4</sub> H	C <sub>3</sub> H <sub>6</sub> (n)	H	H	H
212	Cl	X	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	H
213	Cl	X	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
214	Cl	X	CO <sub>2</sub> H	C <sub>4</sub> H <sub>8</sub> (n)	H	H	COCH <sub>3</sub>
215	Cl	X	CO <sub>2</sub> H	single bond	H	H	COCH <sub>2</sub> Cl
216	Cl	X	CO <sub>2</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>
217	Cl	X	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>
218	Cl	X	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
219	Cl	X	CN <sub>4</sub> H	C <sub>4</sub> H <sub>8</sub> (n)	H	H	COCH <sub>3</sub>
220	Cl	X	CN <sub>4</sub> H	single bond	H	H	COCH <sub>2</sub> Cl
221	Cl	X	CN <sub>4</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>

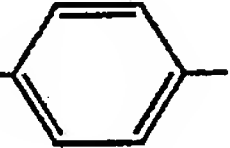
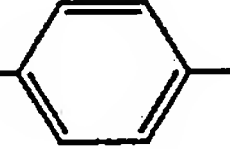
**SUBSTITUTE SHEET**

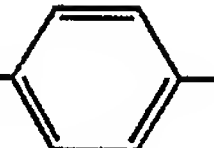
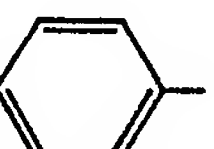
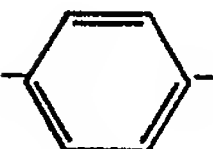
Ex: #	R <sup>1</sup>	R <sup>2</sup>	R <sub>5</sub>	A	B	E	P
222	Cl	X	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>
223	Cl	X	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
224	Cl	X	CO <sub>2</sub> H	C <sub>4</sub> H <sub>8</sub> (n)	H	H	H
225	Cl	X	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	H
226	Cl	X	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
227	Cl	X	CN <sub>4</sub> H	C <sub>4</sub> H <sub>8</sub> (n)	H	H	H
228	Cl	X	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	H
229	Cl	X	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
230	Cl	X	CO <sub>2</sub> H		H	H	COCH <sub>3</sub>
231	Cl	X	CO <sub>2</sub> H	single bond	H	H	COCH <sub>2</sub> Cl
232	Cl	X	CO <sub>2</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>

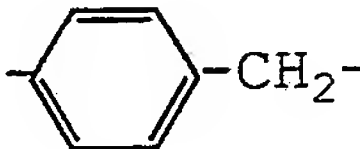
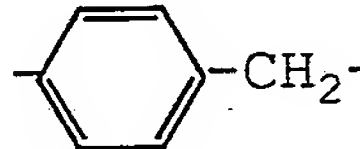
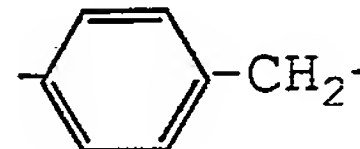
SUBSTITUTE SHEET

Ex: #	R <sup>1</sup>	R <sup>2</sup>	R <sub>5</sub>	A	B	E	P
233	Cl	X	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>
234	Cl	X	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
235	Cl	X	CN <sub>4</sub> H		H	H	COCH <sub>3</sub>
236	Cl	X	CN <sub>4</sub> H	single bond	H	H	COCH <sub>2</sub> Cl
237	Cl	X	CN <sub>4</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>
238	Cl	X	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>
239	Cl	X	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
240	Cl	X	CO <sub>2</sub> H		H	H	H
241	Cl	X	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	H
242	Cl	X	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
243	Cl	X	CN <sub>4</sub> H		H	H	H

**SUBSTITUTE SHEET**


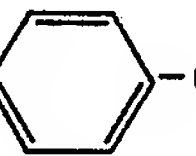
Ex: #	R <sup>1</sup>	R <sup>2</sup>	R <sub>5</sub>	A	B	E	P
244	Cl	X	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	H
245	Cl	X	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
246	Cl	X	CO <sub>2</sub> H	-CH <sub>2</sub> - 	H	H	COCH <sub>3</sub>
247	Cl	X	CO <sub>2</sub> H	single bond	H	H	COCH <sub>2</sub> Cl
248	Cl	X	CO <sub>2</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>
249	Cl	X	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>
250	Cl	X	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
251	Cl	X	CN <sub>4</sub> H	-CH <sub>2</sub> - 	H	H	COCH <sub>3</sub>
252	Cl	X	CN <sub>4</sub> H	single bond	H	H	COCH <sub>2</sub> Cl
253	Cl	X	CN <sub>4</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>
254	Cl	X	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>


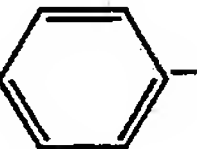
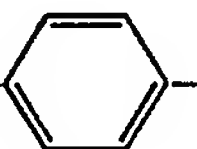
Ex: #	R <sup>1</sup>	R <sup>2</sup>	R <sub>5</sub>	A	B	E	P
255	Cl	X	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
256	Cl	X	CO <sub>2</sub> H	-CH <sub>2</sub> - 	H	H	H
257	Cl	X	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	H
258	Cl	X	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
259	Cl	X	CN <sub>4</sub> H	-CH <sub>2</sub> - 	H	H	H
260	Cl	X	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	H
261	Cl	X	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
262	Cl	X	CO <sub>2</sub> H	 -CH <sub>2</sub> -	H	H	COCH <sub>3</sub>
263	Cl	X	CO <sub>2</sub> H	single bond	H	H	COCH <sub>2</sub> Cl
264	Cl	X	CO <sub>2</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>

Ex: #	R <sup>1</sup>	R <sup>2</sup>	R <sub>5</sub>	A	B	E	P
265	Cl	X	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>
266	Cl	X	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
267	Cl	X	CN <sub>4</sub> H		H	H	COCH <sub>3</sub>
268	Cl	X	CN <sub>4</sub> H	single bond	H	H	COCH <sub>2</sub> Cl
269	Cl	X	CN <sub>4</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>
270	Cl	X	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>
271	Cl	X	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
272	Cl	X	CO <sub>2</sub> H		H	H	H
273	Cl	X	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	H
274	Cl	X	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
275	Cl	X	CN <sub>4</sub> H		H	H	H

SUBSTITUTE SHEET






Ex: #	R <sup>1</sup>	R <sup>2</sup>	R <sub>5</sub>	A	B	E	P
276	Cl	X	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	H
277	Cl	X	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
278	Cl	X	CO <sub>2</sub> H	-CH <sub>2</sub> -  -CH <sub>2</sub> -	H	H	COCH <sub>3</sub>
279	Cl	X	CO <sub>2</sub> H	single bond	H	H	COCH <sub>2</sub> Cl
280	Cl	X	CO <sub>2</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>
281	Cl	X	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>
282	Cl	X	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
283	Cl	X	CN <sub>4</sub> H	-CH <sub>2</sub> -  -CH <sub>2</sub> -	H	H	COCH <sub>3</sub>
284	Cl	X	CN <sub>4</sub> H	single bond	H	H	COCH <sub>2</sub> Cl
285	Cl	X	CN <sub>4</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>
286	Cl	X	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>

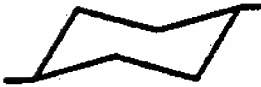

Ex: #	R <sup>1</sup>	R <sup>2</sup>	R <sub>5</sub>	A	B	E	P
287	Cl	X	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
288	Cl	X	CO <sub>2</sub> H	-CH <sub>2</sub> -  -CH <sub>2</sub> -	H	H	H
289	Cl	X	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	H
290	Cl	X	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
291	Cl	X	CN <sub>4</sub> H	-CH <sub>2</sub> -  -CH <sub>2</sub> -	H	H	H
292	Cl	X	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	H
293	Cl	X	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
294	Cl	X	CN <sub>4</sub> H	-CH <sub>2</sub> CH <sub>2</sub> -  -	H	H	COCH <sub>3</sub>
295	Cl	X	CO <sub>2</sub> H	single bond	H	H	COCH <sub>2</sub> Cl
296	Cl	X	CO <sub>2</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>
297	Cl	X	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>

SUBSTITUTE SHEET



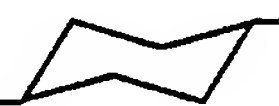
119

Ex: #	R <sup>1</sup>	R <sup>2</sup>	R <sub>5</sub>	A	B	E	P
298	Cl	X	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
299	Cl	X	CN <sub>4</sub> H	-CH <sub>2</sub> CH <sub>2</sub> - 	H	H	H
300	Cl	X	CN <sub>4</sub> H	single bond	H	H	COCH <sub>2</sub> Cl
301	Cl	X	CN <sub>4</sub> H	single bond	H	COC <sub>4</sub> H <sub>9</sub>	
302	Cl	X	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>
303	Cl	X	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
304	Cl	X	CN <sub>4</sub> H	 -CH <sub>2</sub> -CH <sub>2</sub> -H	H	H	COCH <sub>3</sub>
305	Cl	X	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	H
306	Cl	X	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
307	Cl	X	CN <sub>4</sub> H	 -CH <sub>2</sub> -CH <sub>2</sub> -H	H	H	H

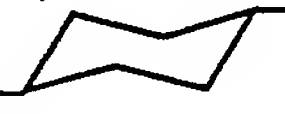
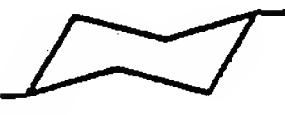
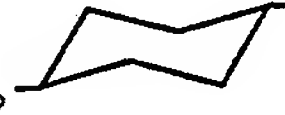
**SUBSTITUTE SHEET**

Ex: #	R <sup>1</sup>	R <sup>2</sup>	R <sub>5</sub>	A	B	E	P
308	Cl	X	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	H
309	Cl	X	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
310	Cl	X	CO <sub>2</sub> H		H	H	COCH <sub>3</sub>
311	Cl	X	CO <sub>2</sub> H	single bond	H	H	COCH <sub>2</sub> Cl
312	Cl	X	CO <sub>2</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>
313	Cl	X	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>
314	Cl	X	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
315	Cl	X	CN <sub>4</sub> H		H	H	COCH <sub>3</sub>
316	Cl	X	CN <sub>4</sub> H	single bond	H	H	COCH <sub>2</sub> Cl
317	Cl	X	CN <sub>4</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>
318	Cl	X	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>

121


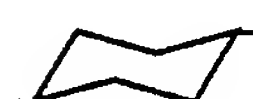
Ex: #	R <sup>1</sup>	R <sup>2</sup>	R <sub>5</sub>	A	B	E	P
319	Cl	X	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
320	Cl	X	CO <sub>2</sub> H		H	H	H
321	Cl	X	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	H
322	Cl	X	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
323	Cl	X	CN <sub>4</sub> H		H	H	H
324	Cl	X	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	H
325	Cl	X	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
326	Cl	X	CO <sub>2</sub> H	-CH <sub>2</sub> - 	H	H	COCH <sub>3</sub>
327	Cl	X	CO <sub>2</sub> H	single bond	H	H	COCH <sub>2</sub> Cl
328	Cl	X	CO <sub>2</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>
329	Cl	X	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>

SUBSTITUTE SHEET



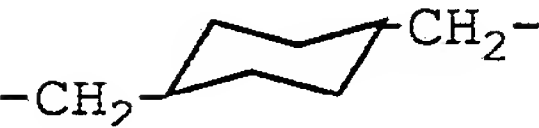
Ex: #	R <sup>1</sup>	R <sup>2</sup>	R <sub>5</sub>	A	B	E	P
330	Cl	X	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
331	Cl	X	CN <sub>4</sub> H	-CH <sub>2</sub> - 	H	H	COCH <sub>3</sub>
332	Cl	X	CN <sub>4</sub> H	single bond	H	H	COCH <sub>2</sub> Cl
333	Cl	X	CN <sub>4</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>
334	Cl	X	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>
335	Cl	X	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
336	Cl	X	CO <sub>2</sub> H	-CH <sub>2</sub> - 	H	H	H
337	Cl	X	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	H
338	Cl	X	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
339	Cl	X	CN <sub>4</sub> H	-CH <sub>2</sub> - 	H	H	H
340	Cl	X	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	H

SUBSTITUTE SHEET

123

Ex: #	R <sup>1</sup>	R <sup>2</sup>	R <sub>5</sub>	A	B	E	P
341	Cl	X	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
342	Cl	X	CO <sub>2</sub> H	 CH <sub>2</sub> -	H	H	COCH <sub>3</sub>
343	Cl	X	CO <sub>2</sub> H	single bond	H	H	COCH <sub>2</sub> Cl
344	Cl	X	CO <sub>2</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>
345	Cl	X	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>
346	Cl	X	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
347	Cl	X	CN <sub>4</sub> H	 CH <sub>2</sub> -	H	H	COCH <sub>3</sub>
348	Cl	X	CN <sub>4</sub> H	single bond	H	H	COCH <sub>2</sub> Cl
349	Cl	X	CN <sub>4</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>
350	Cl	X	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>
351	Cl	X	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>

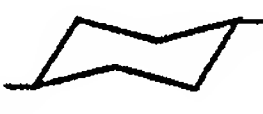

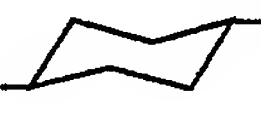
SUBSTITUTE SHEET

Ex: #	R <sup>1</sup>	R <sup>2</sup>	R <sub>5</sub>	A	B	E	P
352	Cl	X	CO <sub>2</sub> H		H	H	H
353	Cl	X	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	H
354	Cl	X	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
355	Cl	X	CN <sub>4</sub> H		H	H	H
356	Cl	X	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	H
357	Cl	X	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
358	Cl	X	CO <sub>2</sub> H		H	H	COCH <sub>3</sub>
359	Cl	X	CO <sub>2</sub> H	single bond	H	H	COCH <sub>2</sub> Cl
360	Cl	X	CO <sub>2</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>
361	Cl	X	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>
362	Cl	X	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>


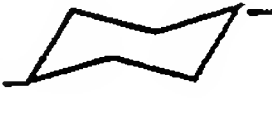
SUBSTITUTE SHEET



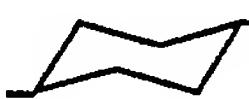
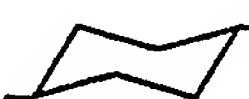
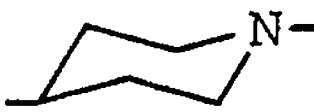
125

Ex: #	R <sup>1</sup>	R <sup>2</sup>	R <sub>5</sub>	A	B	E	P
363	Cl	X	CN <sub>4</sub> H	-CH <sub>2</sub> -  -CH <sub>2</sub> -	H	H	COCH <sub>3</sub>
364	Cl	X	CN <sub>4</sub> H	single bond	H	H	COCH <sub>2</sub> Cl
365	Cl	X	CN <sub>4</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>
366	Cl	X	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>
367	Cl	X	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
368	Cl	X	CO <sub>2</sub> H	-CH <sub>2</sub> -  -CH <sub>2</sub> -	H	H	H
369	Cl	X	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	H
370	Cl	X	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
371	Cl	X	CN <sub>4</sub> H	-CH <sub>2</sub> -  -CH <sub>2</sub> -	H	H	H
372	Cl	X	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	H

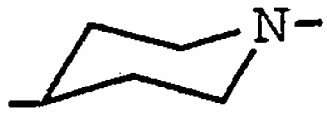


**SUBSTITUTE SHEET**

Ex: #	R <sup>1</sup>	R <sup>2</sup>	R <sub>5</sub>	A	B	E	P
373	Cl	X	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
374	Cl	X	CN <sub>4</sub> H	-CH <sub>2</sub> CH <sub>2</sub> - 	H	H	COCH <sub>3</sub>
375	Cl	X	CO <sub>2</sub> H	single bond	H	H	COCH <sub>2</sub> Cl
376	Cl	X	CO <sub>2</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>
377	Cl	X	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>
378	Cl	X	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
379	Cl	X	CN <sub>4</sub> H	-CH <sub>2</sub> CH <sub>2</sub> - 	H	H	H
380	Cl	X	CN <sub>4</sub> H	single bond	H	H	COCH <sub>2</sub> Cl
381	Cl	X	CN <sub>4</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>
382	Cl	X	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>
383	Cl	X	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>

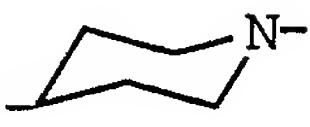
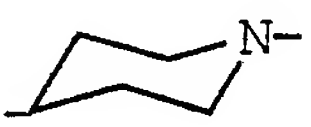
SUBSTITUTE SHEET

Ex: #	R <sup>1</sup>	R <sup>2</sup>	R <sub>5</sub>	A	B	E	P
384	Cl	X	CN <sub>4</sub> H	 CH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>3</sub>
385	Cl	X	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	H
386	Cl	X	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
387	Cl	X	CN <sub>4</sub> H	 CH <sub>2</sub> CH <sub>2</sub> -	H	H	H
388	Cl	X	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	H
389	Cl	X	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
390	Cl	X	CN <sub>4</sub> H		*	H	COCH <sub>3</sub>
391	Cl	X	CO <sub>2</sub> H	single bond	H	H	COCH <sub>2</sub> Cl
392	Cl	X	CO <sub>2</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>
393	Cl	X	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>
394	Cl	X	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>

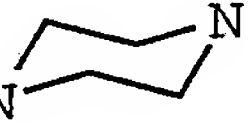
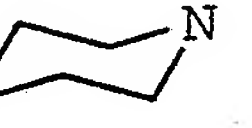

SUBSTITUTE SHEET

Ex: #	R <sup>1</sup>	R <sup>2</sup>	R <sub>5</sub>	A	B	E	P
395	Cl	X	CN <sub>4</sub> H		*	H	H
396	Cl	X	CN <sub>4</sub> H	single bond	H	H	COCH <sub>2</sub> Cl
397	Cl	X	CN <sub>4</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>
398	Cl	X	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>
399	Cl	X	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
400	Cl	X	CN <sub>4</sub> H		*	H	COCH <sub>3</sub>
401	Cl	X	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	H
402	Cl	X	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
403	Cl	X	CN <sub>4</sub> H		*	H	H
404	Cl	X	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	H

SUBSTITUTE SHEET

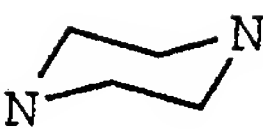
Ex: #	R <sup>1</sup>	R <sup>2</sup>	R <sub>5</sub>	A	B	E	P
405	Cl	X	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
406	Cl	X	CN <sub>4</sub> H	-CH <sub>2</sub> CH <sub>2</sub> - 	*	H	COCH <sub>3</sub>
407	Cl	X	CO <sub>2</sub> H	single bond	H	H	COCH <sub>2</sub> Cl
408	Cl	X	CO <sub>2</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>
409	Cl	X	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>
410	Cl	X	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
411	Cl	X	CN <sub>4</sub> H	-CH <sub>2</sub> -CH <sub>2</sub> - 	*	H	H
412	Cl	X	CN <sub>4</sub> H	single bond	H	H	COCH <sub>2</sub> Cl
413	Cl	X	CN <sub>4</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>
414	Cl	X	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>
415	Cl	X	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>

SUBSTITUTE SHEET

Ex: #	R <sup>1</sup>	R <sup>2</sup>	R <sub>5</sub>	A	B	E	P
416	Cl	X	CN <sub>4</sub> H	-CH <sub>2</sub> -N 	*	H	COCH <sub>3</sub>
417	Cl	X	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	H
418	Cl	X	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
419	Cl	X	CN <sub>4</sub> H	-CH <sub>2</sub> -N 	*	H	H
420	Cl	X	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	H
421	Cl	X	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
422	Cl	X	CN <sub>4</sub> H	-CH <sub>2</sub> -CH <sub>2</sub> -N 	*	H	COCH <sub>3</sub>
423	Cl	X	CN <sub>4</sub> H	single bond	H	H	COCH <sub>2</sub> Cl
424	Cl	X	CN <sub>4</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>
425	Cl	X	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>

SUBSTITUTE SHEET

131

Ex: #	R <sup>1</sup>	R <sup>2</sup>	R <sub>5</sub>	A	B	E	P
426	Cl	X	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
427	Cl	X	CN <sub>4</sub> H	-CH <sub>2</sub> CH <sub>2</sub> -N 	*	H	H
428	Cl	X	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	H
429	Cl	X	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
430	X	Cl	CO <sub>2</sub> H	single bond	H	H	COCH <sub>3</sub>
431	X	Cl	CO <sub>2</sub> H	single bond	H	H	COCH <sub>2</sub> Cl
432	X	Cl	CO <sub>2</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>
433	X	Cl	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>
434	X	Cl	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
435	X	Cl	CN <sub>4</sub> H	single bond	H	H	COCH <sub>3</sub>
436	X	Cl	CN <sub>4</sub> H	single bond	H	H	COCH <sub>2</sub> Cl

SUBSTITUTE SHEET

Ex: #	R <sup>1</sup>	R <sup>2</sup>	R <sub>5</sub>	A	B	E	P
437	X	Cl	CN <sub>4</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>
438	X	Cl	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>
439	X	Cl	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
440	X	Cl	CO <sub>2</sub> H	single bond	H	H	H
441	X	Cl	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	H
442	X	Cl	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
443	X	Cl	CN <sub>4</sub> H	single bond	H	H	H
444	X	Cl	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	H
445	X	Cl	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
446	X	Cl	CO <sub>2</sub> H	-CH <sub>2</sub> -	H	H	COCH <sub>3</sub>
447	X	Cl	CO <sub>2</sub> H	single bond	H	H	COCH <sub>2</sub> Cl

SUBSTITUTE SHEET



Ex: #	R <sup>1</sup>	R <sup>2</sup>	R <sub>5</sub>	A	B	E	P
448	X	Cl	CO <sub>2</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>
449	X	Cl	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>
450	X	Cl	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
451	X	Cl	CN <sub>4</sub> H	single bond	H	H	COCH <sub>2</sub> Cl
452	X	Cl	CN <sub>4</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>
453	X	Cl	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>
454	X	Cl	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
455	X	Cl	CO <sub>2</sub> H	-CH <sub>2</sub> -	H	H	H
456	X	Cl	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	H
457	X	Cl	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
458	X	Cl	CN <sub>4</sub> H	-CH <sub>2</sub> -	H	H	H

134

Ex: #	R <sup>1</sup>	R <sup>2</sup>	R <sub>5</sub>	A	B	E	P
459	X	Cl	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	H
460	X	Cl	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
461	X	Cl	CN <sub>4</sub> H	-CH <sub>2</sub> -	CH <sub>3</sub>	H	H
462	X	Cl	CN <sub>4</sub> H	-CH <sub>2</sub> -	CH <sub>3</sub>	H	COCH <sub>3</sub>
463	X	Cl	CO <sub>2</sub> H	-CH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>3</sub>
464	X	Cl	CO <sub>2</sub> H	single bond	H	H	COCH <sub>2</sub> Cl
465	X	Cl	CO <sub>2</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>
466	X	Cl	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>
467	X	Cl	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
468	X	Cl	CN <sub>4</sub> H	-CH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>3</sub>
469	X	Cl	CN <sub>4</sub> H	single bond	H	H	COCH <sub>2</sub> Cl
470	X	Cl	CN <sub>4</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>

SUBSTITUTE SHEET

135

Ex: #	R <sup>1</sup>	R <sup>2</sup>	R <sub>5</sub>	A	B	E	P
471	X	Cl	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>
472	X	Cl	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
473	X	Cl	CO <sub>2</sub> H	-CH <sub>2</sub> CH <sub>2</sub> -	H	H	H
474	X	Cl	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	H
475	X	Cl	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
476	X	Cl	CN <sub>4</sub> H	-CH <sub>2</sub> CH <sub>2</sub> -	H	H	H
477	X	Cl	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	H
478	X	Cl	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
479	X	Cl	CO <sub>2</sub> H	C <sub>3</sub> H <sub>6</sub> (n)	H	H	COCH <sub>3</sub>
480	X	Cl	CO <sub>2</sub> H	single bond	H	H	COCH <sub>2</sub> Cl
481	X	Cl	CO <sub>2</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>

SUBSTITUTE SHEET


Ex: #	R <sup>1</sup>	R <sup>2</sup>	R <sub>5</sub>	A	B	E	P
482	X	Cl	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>
483	X	Cl	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
484	X	Cl	CN <sub>4</sub> H	C <sub>3</sub> H <sub>6</sub> (n)	H	H	COCH <sub>3</sub>
485	X	Cl	CN <sub>4</sub> H	single bond	H	H	COCH <sub>2</sub> Cl
486	X	Cl	CN <sub>4</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>
487	X	Cl	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>
488	X	Cl	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
489	X	Cl	CO <sub>2</sub> H	C <sub>3</sub> H <sub>6</sub> (n)	H	H	H
490	X	Cl	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	H
491	X	Cl	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
492	X	Cl	CN <sub>4</sub> H	C <sub>3</sub> H <sub>6</sub> (n)	H	H	H

SUBSTITUTE SHEET

137




Ex: #	R <sup>1</sup>	R <sup>2</sup>	R <sub>5</sub>	A	B	E	P
493	X	Cl	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	H
494	X	Cl	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
495	X	Cl	CO <sub>2</sub> H	C <sub>4</sub> H <sub>8</sub> (n)	H	H	COCH <sub>3</sub>
496	X	Cl	CO <sub>2</sub> H	single bond	H	H	COCH <sub>2</sub> Cl
497	X	Cl	CO <sub>2</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>
498	X	Cl	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>
499	X	Cl	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
500	X	Cl	CN <sub>4</sub> H	C <sub>4</sub> H <sub>8</sub> (n)	H	H	COCH <sub>3</sub>
501	X	Cl	CN <sub>4</sub> H	single bond	H	H	COCH <sub>2</sub> Cl
502	X	Cl	CN <sub>4</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>
503	X	Cl	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>

**SUBSTITUTE SHEET**

Ex: #	R <sup>1</sup>	R <sup>2</sup>	R <sub>5</sub>	A	B	E	P
504	X	Cl	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
505	X	Cl	CO <sub>2</sub> H	C <sub>4</sub> H <sub>8</sub> (n)	H	H	H
506	X	Cl	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	H
507	X	Cl	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
508	X	Cl	CN <sub>4</sub> H	C <sub>4</sub> H <sub>8</sub> (n)	H	H	H
509	X	Cl	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	H
510	X	Cl	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
511	X	Cl	CO <sub>2</sub> H		H	H	COCH <sub>3</sub>
512	X	Cl	CO <sub>2</sub> H	single bond	H	H	COCH <sub>2</sub> Cl
513	X	Cl	CO <sub>2</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>
514	X	Cl	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>

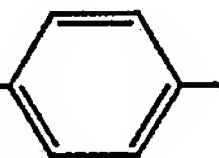
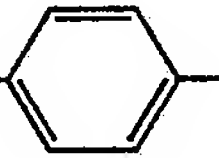
SUBSTITUTE SHEET

139

Ex: #	R <sup>1</sup>	R <sup>2</sup>	R <sub>5</sub>	A	B	E	P
515	X	Cl	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
516	X	Cl	CN <sub>4</sub> H		H	H	COCH <sub>3</sub>
517	X	Cl	CN <sub>4</sub> H	single bond	H	H	COCH <sub>2</sub> Cl
518	X	Cl	CN <sub>4</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>
519	X	Cl	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>
520	X	Cl	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
521	X	Cl	CO <sub>2</sub> H		H	H	H
522	X	Cl	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	H
523	X	Cl	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
524	X	Cl	CN <sub>4</sub> H		H	H	H

SUBSTITUTE SHEET

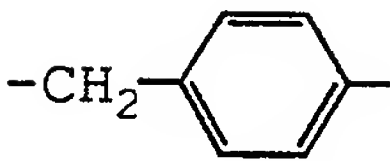
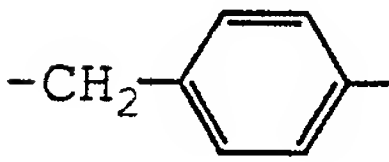
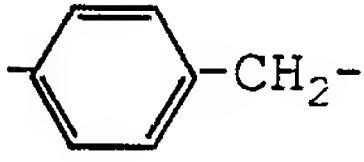
140

Ex: #	R <sup>1</sup>	R <sup>2</sup>	R <sub>5</sub>	A	B	E	P
525	X	Cl	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	H
526	X	Cl	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
527	X	Cl	CO <sub>2</sub> H	-CH <sub>2</sub> - 	H	H	COCH <sub>3</sub>
528	X	Cl	CO <sub>2</sub> H	single bond	H	H	COCH <sub>2</sub> Cl
529	X	Cl	CO <sub>2</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>
530	X	Cl	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>
531	X	Cl	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
532	X	Cl	CN <sub>4</sub> H	-CH <sub>2</sub> - 	H	H	COCH <sub>3</sub>
533	X	Cl	CN <sub>4</sub> H	single bond	H	H	COCH <sub>2</sub> Cl
534	X	Cl	CN <sub>4</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>


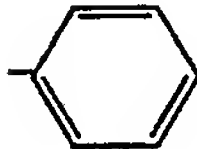
SUBSTITUTE SHEET



141

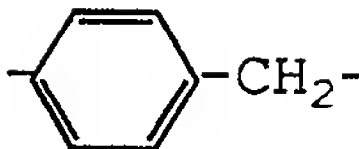

Ex: #	R <sup>1</sup>	R <sup>2</sup>	R <sub>5</sub>	A	B	E	P
535	X	Cl	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>
536	X	Cl	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
537	X	Cl	CO <sub>2</sub> H		H	H	H
538	X	Cl	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	H
539	X	Cl	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
540	X	Cl	CN <sub>4</sub> H		H	H	H
541	X	Cl	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	H
542	X	Cl	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
543	X	Cl	CO <sub>2</sub> H		H	H	COCH <sub>3</sub>
544	X	Cl	CO <sub>2</sub> H	single bond	H	H	COCH <sub>2</sub> Cl

**SUBSTITUTE SHEET**


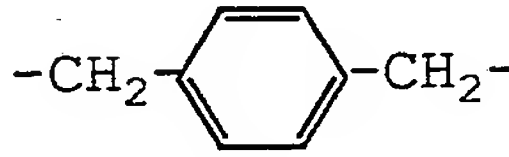

Ex: #	R <sup>1</sup>	R <sup>2</sup>	R <sub>5</sub>	A	B	E	P
545	X	Cl	CO <sub>2</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>
546	X	Cl	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>
547	X	Cl	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
548	X	Cl	CN <sub>4</sub> H	 -CH <sub>2</sub> -	H	H	COCH <sub>3</sub>
549	X	Cl	CN <sub>4</sub> H	single bond	H	H	COCH <sub>2</sub> Cl
550	X	Cl	CN <sub>4</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>
551	X	Cl	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>
552	X	Cl	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
553	X	Cl	CO <sub>2</sub> H	 -CH <sub>2</sub> -	H	H	H
554	X	Cl	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	H

SUBSTITUTE SHEET


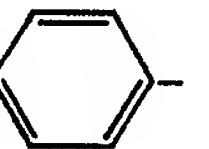
143

Ex: #	R <sup>1</sup>	R <sup>2</sup>	R <sub>5</sub>	A	B	E	P
555	X	Cl	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
556	X	Cl	CN <sub>4</sub> H		H	H	H
557	X	Cl	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	H
558	X	Cl	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
559	X	Cl	CO <sub>2</sub> H		H	H	COCH <sub>3</sub>
560	X	Cl	CO <sub>2</sub> H	single bond	H	H	COCH <sub>2</sub> Cl
561	X	Cl	CO <sub>2</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>
562	X	Cl	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>
563	X	Cl	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>

SUBSTITUTE SHEET

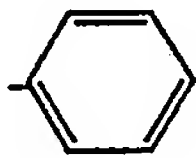
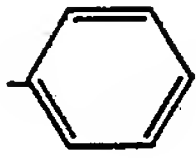
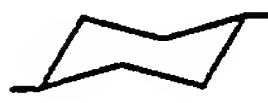
Ex: #	R <sup>1</sup>	R <sup>2</sup>	R <sub>5</sub>	A	B	E	P
564	X	Cl	CN <sub>4</sub> H		H	H	COCH <sub>3</sub>
565	X	Cl	CN <sub>4</sub> H	single bond	H	H	COCH <sub>2</sub> Cl
566	X	Cl	CN <sub>4</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>
567	X	Cl	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>
568	X	Cl	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
569	X	Cl	CO <sub>2</sub> H		H	H	H
570	X	Cl	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	H
571	X	Cl	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
572	X	Cl	CN <sub>4</sub> H		H	H	H
573	X	Cl	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	H

145

Ex: #	R <sup>1</sup>	R <sup>2</sup>	R <sub>5</sub>	A	B	E	P
574	X	Cl	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
575	X	Cl	CN <sub>4</sub> H	-CH <sub>2</sub> CH <sub>2</sub> - 	H	H	COCH <sub>3</sub>
576	X	Cl	CO <sub>2</sub> H	single bond	H	H	COCH <sub>2</sub> Cl
577	X	Cl	CO <sub>2</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>
578	X	Cl	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>
579	X	Cl	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
580	X	Cl	CN <sub>4</sub> H	-CH <sub>2</sub> CH <sub>2</sub> - 	H	H	H
581	X	Cl	CN <sub>4</sub> H	single bond	H	H	COCH <sub>2</sub> Cl
582	X	Cl	CN <sub>4</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>
583	X	Cl	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>

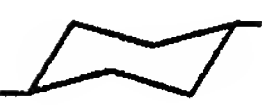
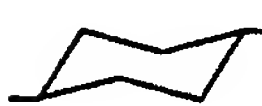
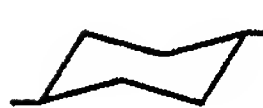
SUBSTITUTE SHEET

146

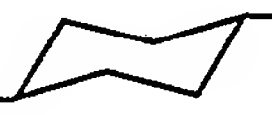
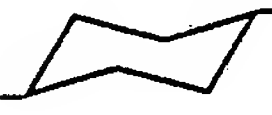
Ex: #	R <sup>1</sup>	R <sup>2</sup>	R <sub>5</sub>	A	B	E	P
584	X	Cl	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
585	X	Cl	CN <sub>4</sub> H	 -CH <sub>2</sub> -CH <sub>2</sub> -	H	H	COCH <sub>3</sub>
586	X	Cl	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	H
587	X	Cl	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
588	X	Cl	CN <sub>4</sub> H	 -CH <sub>2</sub> -CH <sub>2</sub> -	H	H	H
589	X	Cl	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	H
590	X	Cl	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
591	X	Cl	CO <sub>2</sub> H		H	H	COCH <sub>3</sub>
592	X	Cl	CO <sub>2</sub> H	single bond	H	H	COCH <sub>2</sub> Cl
593	X	Cl	CO <sub>2</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>

SUBSTITUTE SHEET

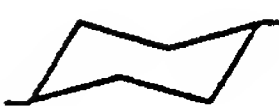
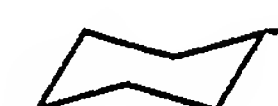

147

Ex: #	R <sup>1</sup>	R <sup>2</sup>	R <sub>5</sub>	A	B	E	P
594	X	Cl	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>
595	X	Cl	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
596	X	Cl	CN <sub>4</sub> H		H	H	COCH <sub>3</sub>
597	X	Cl	CN <sub>4</sub> H	single bond	H	H	COCH <sub>2</sub> Cl
598	X	Cl	CN <sub>4</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>
599	X	Cl	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>
600	X	Cl	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
601	X	Cl	CO <sub>2</sub> H		H	H	H
602	X	Cl	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	H
603	X	Cl	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
604	X	Cl	CN <sub>4</sub> H		H	H	H

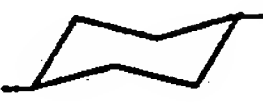

SUBSTITUTE SHEET

Ex: #	R <sup>1</sup>	R <sup>2</sup>	R <sub>5</sub>	A	B	E	P
605	X	Cl	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	H
606	X	Cl	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
607	X	Cl	CO <sub>2</sub> H	-CH <sub>2</sub> - 	H	H	COCH <sub>3</sub>
608	X	Cl	CO <sub>2</sub> H	single bond	H	H	COCH <sub>2</sub> Cl
609	X	Cl	CO <sub>2</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>
610	X	Cl	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>
611	X	Cl	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
612	X	Cl	CN <sub>4</sub> H	-CH <sub>2</sub> - 	H	H	COCH <sub>3</sub>
613	X	Cl	CN <sub>4</sub> H	single bond	H	H	COCH <sub>2</sub> Cl
614	X	Cl	CN <sub>4</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>
615	X	Cl	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>

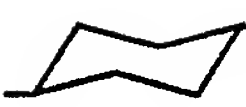
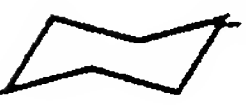



Ex: #	R <sup>1</sup>	R <sup>2</sup>	R <sub>5</sub>	A	B	E	P
616	X	Cl	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
617	X	Cl	CO <sub>2</sub> H	-CH <sub>2</sub> - 	H	H	H
618	X	Cl	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	H
619	X	Cl	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
620	X	Cl	CN <sub>4</sub> H	-CH <sub>2</sub> - 	H	H	H
621	X	Cl	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	H
622	X	Cl	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
623	X	Cl	CO <sub>2</sub> H	 -CH <sub>2</sub> -	H	H	COCH <sub>3</sub>
624	X	Cl	CO <sub>2</sub> H	single bond	H	H	COCH <sub>2</sub> Cl
625	X	Cl	CO <sub>2</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>

SUBSTITUTE SHEET

Ex: #	R <sup>1</sup>	R <sup>2</sup>	R <sub>5</sub>	A	B	E	P
626	X	Cl	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>
627	X	Cl	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
628	X	Cl	CN <sub>4</sub> H	 CH <sub>2</sub> -	H	H	COCH <sub>3</sub>
629	X	Cl	CN <sub>4</sub> H	single bond	H	H	COCH <sub>2</sub> Cl
630	X	Cl	CN <sub>4</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>
631	X	Cl	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>
632	X	Cl	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
633	X	Cl	CO <sub>2</sub> H	 CH <sub>2</sub> -	H	H	H
634	X	Cl	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	H
635	X	Cl	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H

SUBSTITUTE SHEET

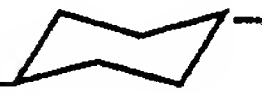

Ex: #	R <sup>1</sup>	R <sup>2</sup>	R <sub>5</sub>	A	B	E	P
636	X	Cl	CN <sub>4</sub> H	 CH <sub>2</sub> -	H	H	H
637	X	Cl	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	H
638	X	Cl	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
639	X	Cl	CO <sub>2</sub> H	-CH <sub>2</sub> -  CH <sub>2</sub> -	H	H	COCH <sub>3</sub>
640	X	Cl	CO <sub>2</sub> H	single bond	H	H	COCH <sub>2</sub> Cl
641	X	Cl	CO <sub>2</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>
642	X	Cl	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>
643	X	Cl	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
644	X	Cl	CN <sub>4</sub> H	-CH <sub>2</sub> -  CH <sub>2</sub> -	H	H	COCH <sub>3</sub>
645	X	Cl	CN <sub>4</sub> H	single bond	H	H	COCH <sub>2</sub> Cl

SUBSTITUTE SHEET

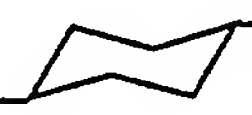
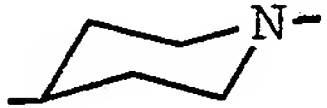
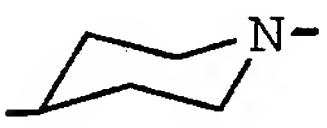
Ex: #	R <sup>1</sup>	R <sup>2</sup>	R <sub>5</sub>	A	B	E	P
646	X	Cl	CN <sub>4</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>
647	X	Cl	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>
648	X	Cl	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
649	X	Cl	CO <sub>2</sub> H	$-\text{CH}_2-\text{cyclohexane}-\text{CH}_2-$	H	H	H
650	X	Cl	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	H
651	X	Cl	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
652	X	Cl	CN <sub>4</sub> H	$-\text{CH}_2-\text{cyclohexane}-\text{CH}_2-$	H	H	H
653	X	Cl	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	H
654	X	Cl	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
655	X	Cl	CN <sub>4</sub> H	$-\text{CH}_2\text{CH}_2-\text{cyclohexane}-$	H	H	COCH <sub>3</sub>
656	X	Cl	CO <sub>2</sub> H	single bond	H	H	COCH <sub>2</sub> Cl

SUBSTITUTE SHEET

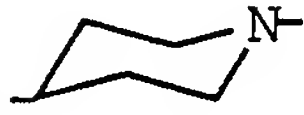
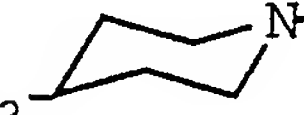
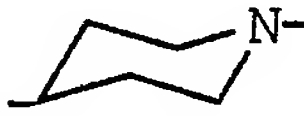
153

Ex: #	R <sup>1</sup>	R <sup>2</sup>	R <sub>5</sub>	A	B	E	P
657	X	Cl	CO <sub>2</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>
658	X	Cl	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>
659	X	Cl	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
660	X	Cl	CN <sub>4</sub> H	-CH <sub>2</sub> CH <sub>2</sub> - 	H	H	H
661	X	Cl	CN <sub>4</sub> H	single bond	H	H	COCH <sub>2</sub> Cl
662	X	Cl	CN <sub>4</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>
663	X	Cl	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>
664	X	Cl	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
665	X	Cl	CN <sub>4</sub> H	 CH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>3</sub>
666	X	Cl	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	H


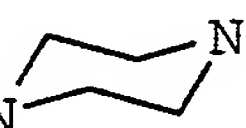
SUBSTITUTE SHEET

Ex: #	R <sup>1</sup>	R <sup>2</sup>	R <sub>5</sub>	A	B	E	P
667	X	Cl	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
668	X	Cl	CN <sub>4</sub> H	 CH <sub>2</sub> CH <sub>2</sub> -	H	H	H
669	X	Cl	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	H
670	X	Cl	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
671	X	Cl	CN <sub>4</sub> H		*	H	COCH <sub>3</sub>
672	X	Cl	CO <sub>2</sub> H	single bond	H	H	COCH <sub>2</sub> Cl
673	X	Cl	CO <sub>2</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>
674	X	Cl	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>
675	X	Cl	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
676	X	Cl	CN <sub>4</sub> H		*	H	H
677	X	Cl	CN <sub>4</sub> H	single bond	H	H	COCH <sub>2</sub> Cl

SUBSTITUTE SHEET

Ex: #	R <sup>1</sup>	R <sup>2</sup>	R <sub>5</sub>	A	B	E	P
678	X	Cl	CN <sub>4</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>
679	X	Cl	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>
680	X	Cl	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
681	X	Cl	CN <sub>4</sub> H	-CH <sub>2</sub> - 	*	H	COCH <sub>3</sub>
682	X	Cl	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	H
683	X	Cl	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
684	X	Cl	CN <sub>4</sub> H	-CH <sub>2</sub> - 	*	H	H
685	X	Cl	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	H
686	X	Cl	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
687	X	Cl	CN <sub>4</sub> H	-CH <sub>2</sub> CH <sub>2</sub> - 	*	H	COCH <sub>3</sub>

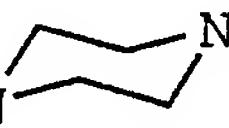
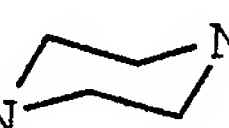
SUBSTITUTE SHEET

Ex: #	R <sup>1</sup>	R <sup>2</sup>	R <sub>5</sub>	A	B	E	P
688	X	Cl	CO <sub>2</sub> H	single bond	H	H	COCH <sub>2</sub> Cl
689	X	Cl	CO <sub>2</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>
690	X	Cl	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>
691	X	Cl	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
692	X	Cl	CN <sub>4</sub> H	-CH <sub>2</sub> -CH <sub>2</sub> - 	*	H	H
693	X	Cl	CN <sub>4</sub> H	single bond	H	H	COCH <sub>2</sub> Cl
694	X	Cl	CN <sub>4</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>
695	X	Cl	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>
696	X	Cl	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
697	X	Cl	CN <sub>4</sub> H	-CH <sub>2</sub> -N- 	*	H	COCH <sub>3</sub>

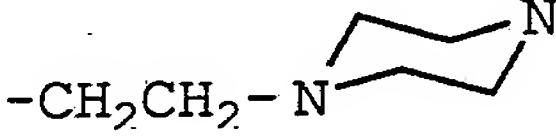
SUBSTITUTE SHEET



157

Ex: #	R <sup>1</sup>	R <sup>2</sup>	R <sub>5</sub>	A	B	E	P
698	X	Cl	CO <sub>2</sub> H	single bond	H	CH <sub>3</sub>	H
699	X	Cl	CO <sub>2</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
700	X	Cl	CN <sub>4</sub> H	-CH <sub>2</sub> -N 	*	H	H
701	X	Cl	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	H
702	X	Cl	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H
703	X	Cl	CN <sub>4</sub> H	-CH <sub>2</sub> -CH <sub>2</sub> -N 	*	H	COCH <sub>3</sub>
704	X	Cl	CN <sub>4</sub> H	single bond	H	H	COCH <sub>2</sub> Cl
705	X	Cl	CN <sub>4</sub> H	single bond	H	H	COC <sub>4</sub> H <sub>9</sub>
706	X	Cl	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	COCH <sub>3</sub>
707	X	Cl	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>

SUBSTITUTE SHEET

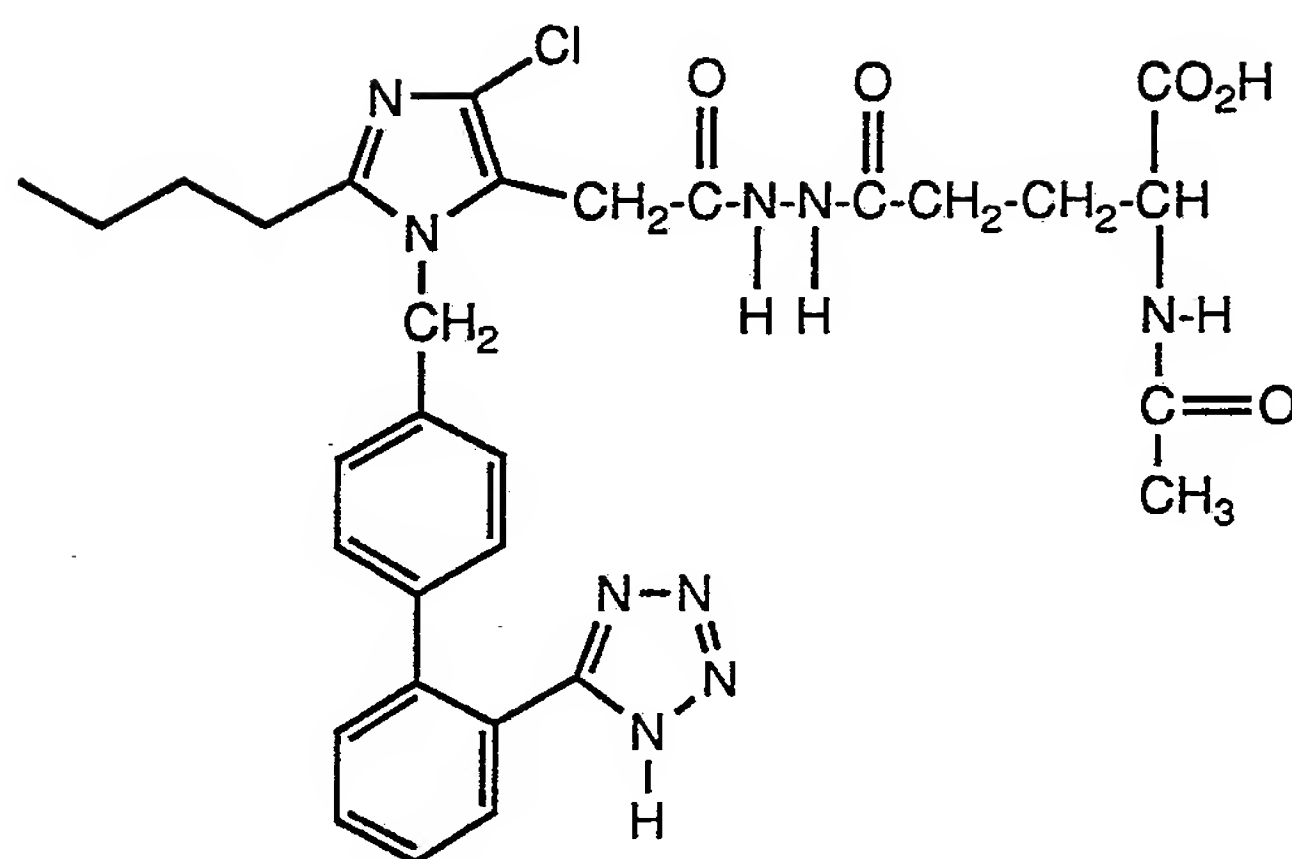
Ex: #	R <sup>1</sup>	R <sup>2</sup>	R <sub>5</sub>	A	B	E	P
708	X	Cl	CN <sub>4</sub> H		*	H	H
709	X	Cl	CN <sub>4</sub> H	single bond	H	CH <sub>3</sub>	H
710	X	Cl	CN <sub>4</sub> H	single bond	H	C <sub>2</sub> H <sub>5</sub>	H

\*B is incorporated in A

Another class of highly preferred specific  
conjugates of the invention is provided by conjugates  
formed from a biphenylmethyl 1H-substituted imidazole AII  
antagonist compound having a terminal carboxyl group  
5 attached to the imidazo nucleus. In this family of  
conjugates, the cleavable glutamyl residue is attached  
through a diamino linker moiety which connects the imidazo  
AII antagonist terminal carboxylic moiety through two amide  
bonds to the gamma carbon of the glutamyl residue. Such  
10 conjugates are shown as Examples 711-1526. General  
procedures for preparation of the conjugates of Examples  
#711-#1526 are described in Schemes VI-VII. Detailed  
procedures for preparation of representative conjugates are  
described in Examples #711 and #712. Procedures similar to  
15 these aforementioned general and specific procedures may be  
used for preparation of the conjugates identified as  
Examples #711-#1526 shown in Table VII.

20

## Example 711



5 N-acetyl-L-glutamic acid, 5-[2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazol-5-yl]acetylhydrazide

Step 1: Preparation of 2-butyl-5-cyanomethyl-4-chloro-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-methyl]imidazole.

10 Thionyl chloride (7.2 mL, 98 mmol) is slowly dripped into a solution of 8.45 g (20.0 mmol) of the compound of Example 78 in a minimum of chloroform. The mixture is stirred for 2 h at ambient temperature and the solvent is removed in vacuo. The chloride is dissolved in

15 dimethylsulfoxide (DMSO) and is added to a solution of 5.80 g (118 mmol) of sodium cyanide in 400 mL of DMSO. The solution is stirred overnight under nitrogen at ambient temperature; water is added and the aqueous layer is extracted with ethyl acetate. The extracts are combined, are dried (MgSO<sub>4</sub>), and

20 are concentrated in vacuo to give the crude product. Purification by silica gel chromatography (Waters DeltaPrep-500A) provides the pure 5-cyanomethyl derivative.

Step 2: Preparation of 2-butyl-5-carboxymethyl-4-chloro-1-  
[(2'-(1H-tetrazol-5-yl)biphenyl-4-methyl)imidazole.

A solution of 6.5 g (15 mmol) of the 5-cyanomethyl  
5 derivative from step 1 in 150 mL of concentrated hydrochloric  
acid/acetic acid (1:1) is stirred at reflux overnight. The  
solvents are removed in vacuo to give the crude product.  
Purification by reverse phase chromatography (Waters  
Deltaprep-3000) provides the pure 5-acetic acid derivative.

10

Step 3: Preparation of 2-butyl-4-chloro-5-  
methoxycarbonylmethyl-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-  
methyl)imidazole.

15 A solution of 4.5 g (10 mmol) of the 5-acetic acid  
derivative from step 2 in 150 mL of absolute methanol is  
cooled to -10°C and is treated with 1.5 mL (20 mmol) of  
thionyl chloride under nitrogen. The reaction is allowed to  
warm to ambient temperature and is stirred at reflux  
20 overnight. The methanol is removed in vacuo and the crude  
product is dissolved in water. The pH is adjusted to pH 4  
with 1N NaOH and the solution is extracted with ethyl acetate.  
The extracts are combined, are dried (MgSO<sub>4</sub>), and are  
concentrated in vacuo to give the crude product. Purification  
25 by silica gel chromatography (Waters Prep-500A) provides the  
pure 5-methyl acetate derivative.

Step 4: Preparation of 2-butyl-4-chloro-5-hydrazinylcarbonyl-  
methyl-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-methyl)imidazole.

30

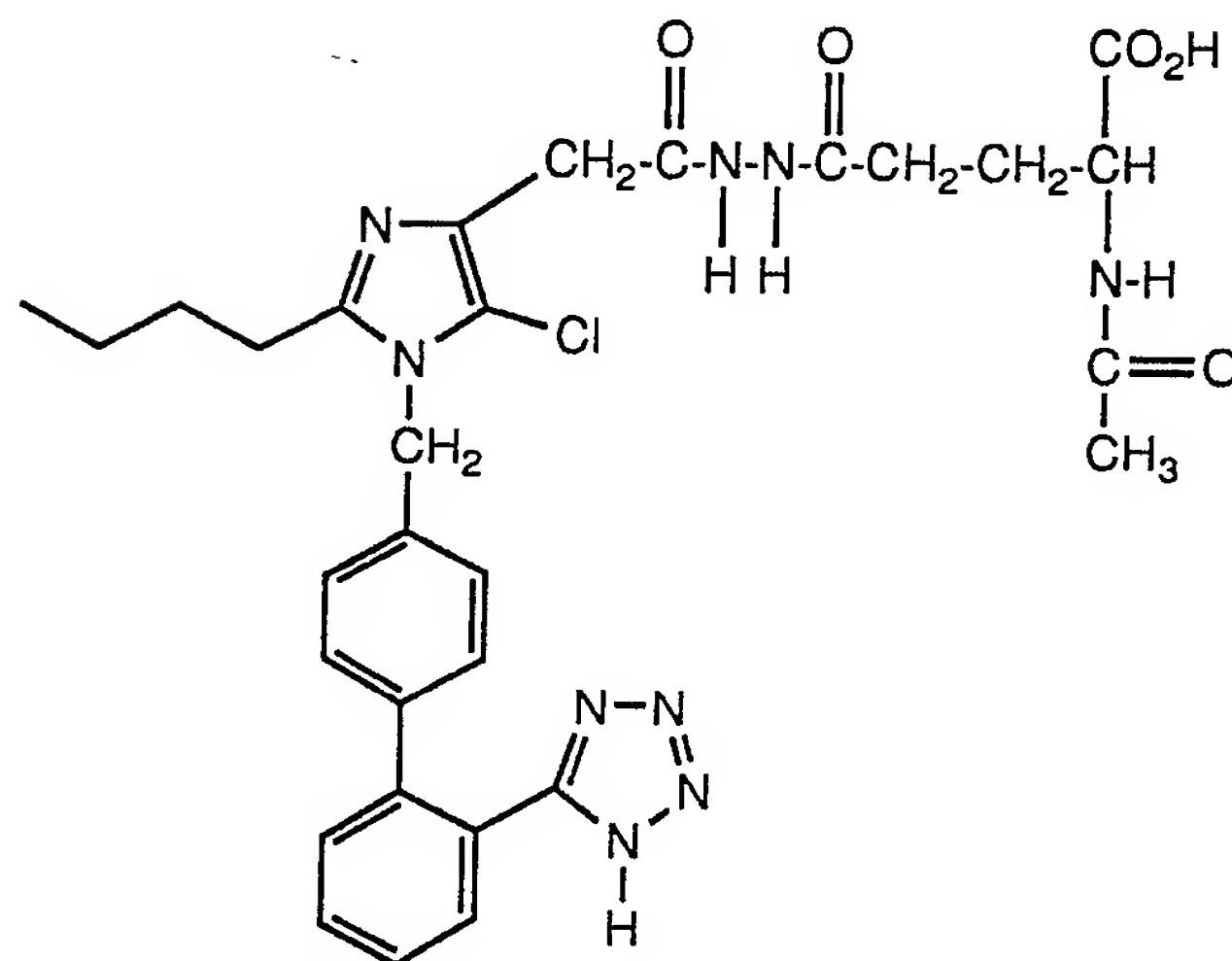
Under nitrogen, 2.32 g (5.0 mmol) of the 5-methyl  
acetate derivative from step 3 is dissolved in 50 mL of  
methanol and is treated with 5mL (160 mmol) of anhydrous  
hydrazine. The reaction is allowed to stir at reflux

overnight; concentration in vacuo gives the crude material. Purification by silica gel chromatography (Waters Prep-500A) provides the pure 5-acetic acid hydrazide derivative.

5 Step 5: Preparation of N-acetyl-L-glutamic acid, 5-[2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)][1,1'-biphenyl]-4-yl]methyl]-1H-imidazol-5-yl]acetylhydrazide

10 To a solution of 1.70 g (5.6 mmol) of N-Boc-L-glutamic acid- $\alpha$ -tertbutyl ester (BACHEM) in 50 mL of methylene chloride under nitrogen is added 580 mg (2.8 mmol) of solid dicyclohexylcarbodiimide (DCC). The reaction is allowed to stir for 2 h and is filtered under nitrogen. The anhydride solution is then added to a solution of 1.01 g (2.4 mmol) of  
15 the hydrazide from step 4 in 75 mL of methylene chloride under nitrogen. The reaction is stirred overnight, is concentrated to a volume of 25 mL, is cooled to 0°C, and is treated with 25 mL of TFA under nitrogen. The stirred reaction is allowed to warm to ambient temperature overnight and is concentrated in  
20 vacuo. The crude product is dissolved in 100 mL of acetonitrile/water (1:1) and the pH is adjusted to 8 with 1 M K<sub>2</sub>CO<sub>3</sub>. The solution is cooled to 0°C and 0.23 mL (2.4 mmol) of acetic anhydride and 2.4 mL (2.4 mmol) of 1 M K<sub>2</sub>CO<sub>3</sub> is added every 30 min for 5 h; the pH is maintained at 9 and the  
25 reaction temperature is kept below 5°C. After the last addition, the reaction is allowed to warm to ambient temperature overnight. The pH is adjusted to 4 with 3 M HCl and the reaction is concentrated to 100 mL. Purification by reverse phase chromatography (Waters Deltaprep-3000) gives the  
30 pure product.

## Example 712



N-acetyl-L-glutamic acid, 5-[2-butyl-5-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazol-4-yl]acetylhydrazide

Step 1: Preparation of 2-butyl-4-cyanomethyl-5-chloro-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-methyl]imidazole.

Thionyl chloride (7.2 mL, 98 mmol) is slowly dripped into a solution of 8.45 g (20.0 mmol) of the compound of Example 79 in a minimum of chloroform. The mixture is stirred for 2 h at ambient temperature and the solvent is removed in vacuo. The chloride is dissolved in DMSO and is added to a solution of 5.80 g (118 mmol) of sodium cyanide in 400 mL of DMSO. The solution is stirred overnight under nitrogen at ambient temperature; water is added and the aqueous layer is extracted with ethyl acetate. The extracts are combined, are dried (MgSO<sub>4</sub>), and are concentrated in vacuo to give the crude product. Purification by silica gel chromatography (Waters Prep-500A) provides the pure 4-cyanomethyl derivative.

Step 2: Preparation of 2-butyl-4-carboxymethyl-5-chloro-1-  
[(2'-(1H-tetrazol-5-yl)biphenyl-4-methyl)imidazole.

5                   A solution of 6.5 g (15 mmol) of the 4-cyanomethyl  
derivative from step 1 in 150 mL of concentrated hydrochloric  
acid/acetic acid (1:1) is stirred at reflux overnight. The  
solvents are removed in vacuo to give the crude product.  
Purification by reverse phase chromatography provides (Waters  
10 Deltaprep-3000) the pure 4-acetic acid derivative.

Step 3: Preparation of 2-butyl-5-chloro-4-methoxycarbonyl-  
methyl-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-methyl)imidazole.

15                   A solution of 4.5 g (10 mmol) of the 4-acetic acid  
derivative from step 2 in 150 mL of absolute methanol is  
cooled to -10°C and is treated with 1.5 mL (20 mmol) of  
thionyl chloride under nitrogen. The reaction is allowed to  
warm to ambient temperature and is stirred at reflux  
20 overnight. The methanol is removed in vacuo and the crude  
product is dissolved in water. The pH is adjusted to pH 4  
with 1N NaOH and the solution is extracted with ethyl acetate.  
The extracts are combined, are dried (MgSO<sub>4</sub>), and are  
concentrated in vacuo to give the crude product. Purification  
25 by silica gel chromatography (Waters Prep-500A) provides the  
pure 4-methyl acetate derivative.

Step 4: Preparation of 2-butyl-5-chloro-4-hydrazinylcarbonyl-  
methyl-1-[(2'-(1H-tetrazole-5-yl)biphenyl-4-methyl)imidazole.

30                   Under nitrogen, 2.32 g (5.0 mmol) of the 4-methyl  
acetate derivative from step 3 is dissolved in 50 mL of  
methanol and is treated with 5 mL (160 mmol) of anhydrous  
hydrazine. The reaction is allowed to stir at reflux

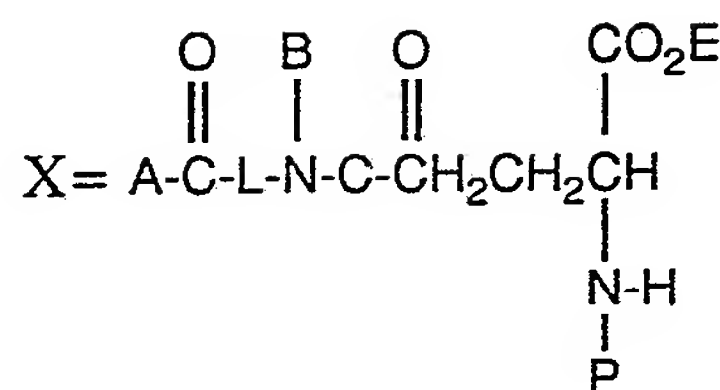
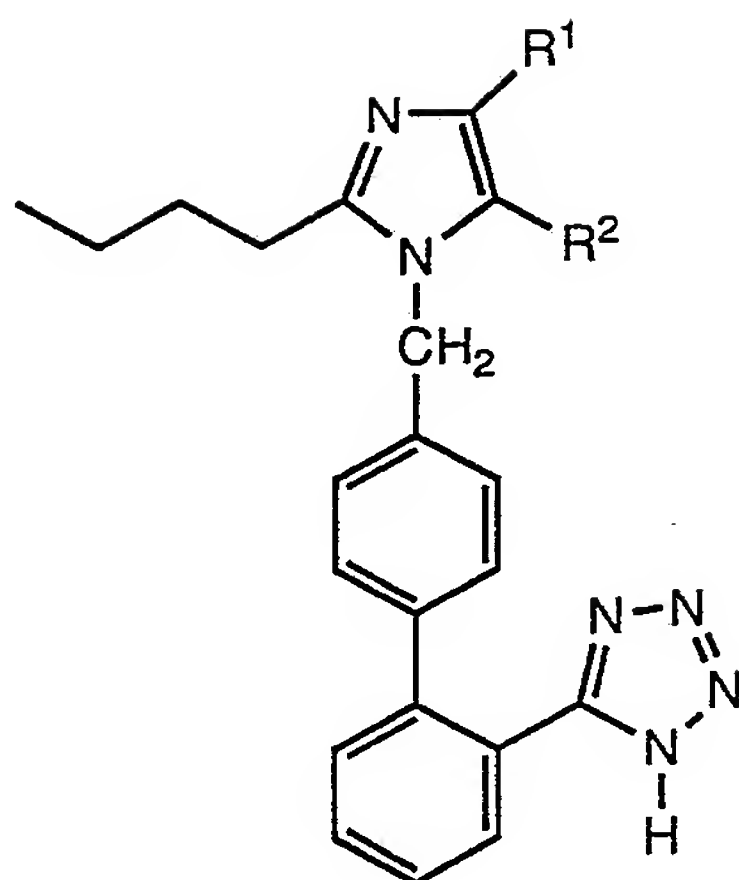


overnight; concentration in vacuo gives the crude material.  
Purification by silica gel chromatography (Waters Prep-500A)  
provides the pure 4-acetic acid hydrazide derivative.



5 Step 5: Preparation of N-acetyl-L-glutamic acid, 5-[2-butyl-5-chloro-1-[[2'-(1H-tetrazol-5-yl)][1,1'-biphenyl]-4-yl]methyl]-1H-imidazol-4-yl]acetylhydrazide

To a solution of 1.70 g (5.6 mmol) of N-Boc-L-glutamic acid- $\alpha$ -tertbutyl ester (BACHEM) in 50 mL of methylene chloride under nitrogen is added 580 mg (2.8 mmol) of solid dicyclohexylcarbodiimide (DCC). The reaction is allowed to stir for 2 h and is filtered under nitrogen. The anhydride solution is then added to a solution of 1.01 g (2.4 mmol) of the hydrazide from step 4 in 75 mL of methylene chloride under nitrogen. The reaction is stirred overnight, is concentrated to a volume of 25 mL, is cooled to 0°C, and is treated with 25 mL of TFA under nitrogen. The stirred reaction is allowed to warm to ambient temperature overnight and is concentrated in vacuo. The crude product is dissolved in 100 mL of acetonitrile/water (1:1) and the pH is adjusted to 8 with 1 M K<sub>2</sub>CO<sub>3</sub>. The solution is cooled to 0°C and 0.23 mL (2.4 mmol) of acetic anhydride and 2.4 mL (2.4 mmol) of 1 M K<sub>2</sub>CO<sub>3</sub> is added every 30 min for 5 h; the pH is maintained at 9 and the reaction temperature is kept below 5°C. After the last addition, the reaction is allowed to warm to ambient temperature overnight. The pH is adjusted to 4 with 3 M HCl and the reaction is concentrated to 100 mL. Purification by reverse phase chromatography (Waters Deltaprep-3000) gives the pure product.


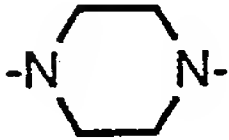
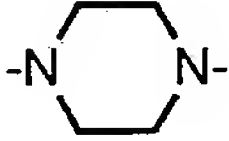
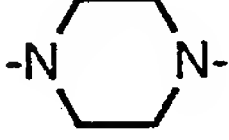
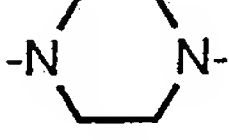
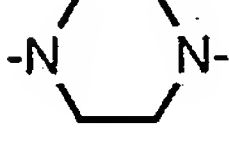
TABLE VII



Ex. #	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
713	Cl	X	single bond	-NH-	H	H	COCH <sub>3</sub>
714	Cl	X	single bond	-NH-	H	H	COCH <sub>2</sub> Cl
715	Cl	X	single bond	-NH-	H	H	COC <sub>4</sub> H <sub>9</sub>
716	Cl	X	single bond	-NH-	H	CH <sub>3</sub>	COCH <sub>3</sub>
717	Cl	X	single bond	-NH-	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
718	Cl	X	single bond	-NH-	H	H	H
719	Cl	X	single bond	-NH-	H	CH <sub>3</sub>	H
720	Cl	X	single bond	-NH-	H	C <sub>2</sub> H <sub>5</sub>	H

Ex. #	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
721	Cl	X	single bond	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>3</sub>
722	Cl	X	single bond	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>2</sub> Cl
723	Cl	X	single bond	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COC <sub>4</sub> H <sub>9</sub>
724	Cl	X	single bond	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	CH <sub>3</sub>	COCH <sub>3</sub>
725	Cl	X	single bond	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
726	Cl	X	single bond	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	H
727	Cl	X	single bond	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	CH <sub>3</sub>	H
728	Cl	X	single bond	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	C <sub>2</sub> H <sub>5</sub>	H
729	Cl	X	single bond		*	H	COCH <sub>3</sub>
730	Cl	X	single bond		H	H	COCH <sub>2</sub> Cl

SUBSTITUTE SHEET

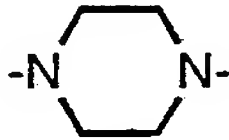
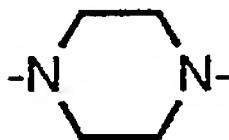

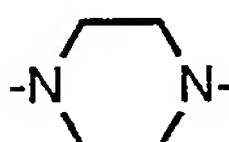
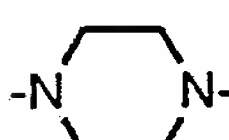
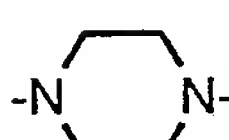
Ex. #	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
731	Cl	X	single bond		H	H	COC <sub>4</sub> H <sub>9</sub>
732	Cl	X	single bond		H	CH <sub>3</sub>	COCH <sub>3</sub>
733	Cl	X	single bond		H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
734	Cl	X	single bond		*	H	H
735	Cl	X	single bond		H	CH <sub>3</sub>	H
736	Cl	X	single bond		H	C <sub>2</sub> H <sub>5</sub>	H
737	Cl	X	CH <sub>2</sub>	-NH-	H	H	COCH <sub>2</sub> Cl
738	Cl	X	CH <sub>2</sub>	-NH-	H	H	COC <sub>4</sub> H <sub>9</sub>

SUBSTITUTE SHEET

Ex. #	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
739	Cl	X	CH <sub>2</sub>	-NH-	H	CH <sub>3</sub>	COCH <sub>3</sub>
740	Cl	X	CH <sub>2</sub>	-NH-	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
741	Cl	X	CH <sub>2</sub>	-NH-	H	H	H
742	Cl	X	CH <sub>2</sub>	-NH-	H	CH <sub>3</sub>	H
743	Cl	X	CH <sub>2</sub>	-NH-	H	C <sub>2</sub> H <sub>5</sub>	H
744	Cl	X	CH <sub>2</sub>	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>3</sub>
745	Cl	X	CH <sub>2</sub>	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>2</sub> Cl
746	Cl	X	CH <sub>2</sub>	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COC <sub>4</sub> H <sub>9</sub>
747	Cl	X	CH <sub>2</sub>	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	CH <sub>3</sub>	COCH <sub>3</sub>
748	Cl	X	CH <sub>2</sub>	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
749	Cl	X	CH <sub>2</sub>	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	H

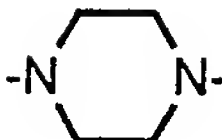
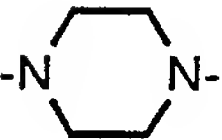
SUBSTITUTE SHEET

170


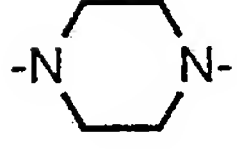
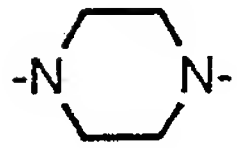
Ex. #	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
750	Cl	X	CH <sub>2</sub>	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	CH <sub>3</sub>	H
751	Cl	X	CH <sub>2</sub>	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	C <sub>2</sub> H <sub>5</sub>	H
752	Cl	X	CH <sub>2</sub>		*	H	COCH <sub>3</sub>
753	Cl	X	CH <sub>2</sub>		H	H	COCH <sub>2</sub> Cl
754	Cl	X	CH <sub>2</sub>		H	H	COC <sub>4</sub> H <sub>9</sub>
755	Cl	X	CH <sub>2</sub>		H	CH <sub>3</sub>	COCH <sub>3</sub>
756	Cl	X	CH <sub>2</sub>		H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
757	Cl	X	CH <sub>2</sub>		*	H	H

SUBSTITUTE SHEET

171

Ex. #	R <sup>1</sup>	R <sup>2</sup>	A	L	B E	P
758	Cl	X	CH <sub>2</sub>		H CH <sub>3</sub>	H
759	Cl	X	CH <sub>2</sub>		H C <sub>2</sub> H <sub>5</sub>	H
760	Cl	X	CH <sub>2</sub> CH <sub>2</sub>	-NH-	H H	COCH <sub>3</sub>
761	Cl	X	CH <sub>2</sub> CH <sub>2</sub>	-NH-	H H	COCH <sub>2</sub> Cl
762	Cl	X	CH <sub>2</sub> CH <sub>2</sub>	-NH-	H H	COC <sub>4</sub> H <sub>9</sub>
763	Cl	X	CH <sub>2</sub> CH <sub>2</sub>	-NH-	H CH <sub>3</sub>	COCH <sub>3</sub>
764	Cl	X	CH <sub>2</sub> CH <sub>2</sub>	-NH-	H C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
765	Cl	X	CH <sub>2</sub> CH <sub>2</sub>	-NH-	H H	H
766	Cl	X	CH <sub>2</sub> CH <sub>2</sub>	-NH-	H CH <sub>3</sub>	H
767	Cl	X	CH <sub>2</sub> CH <sub>2</sub>	-NH-	H C <sub>2</sub> H <sub>5</sub>	H
768	Cl	X	CH <sub>2</sub> CH <sub>2</sub>	-NHCH <sub>2</sub> CH <sub>2</sub> -	H H	COCH <sub>3</sub>



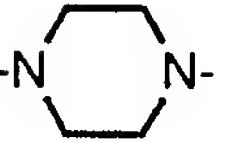
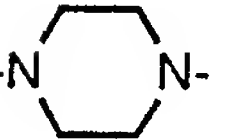

SUBSTITUTE SHEET

Ex. #	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
769	Cl	X	CH <sub>2</sub> CH <sub>2</sub>	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>2</sub> Cl
770	Cl	X	CH <sub>2</sub> CH <sub>2</sub>	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COC <sub>4</sub> H <sub>9</sub>
771	Cl	X	CH <sub>2</sub> CH <sub>2</sub>	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	CH <sub>3</sub>	COCH <sub>3</sub>
772	Cl	X	CH <sub>2</sub> CH <sub>2</sub>	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
773	Cl	X	CH <sub>2</sub> CH <sub>2</sub>	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	H
774	Cl	X	CH <sub>2</sub> CH <sub>2</sub>	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	CH <sub>3</sub>	H
775	Cl	X	CH <sub>2</sub> CH <sub>2</sub>	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	C <sub>2</sub> H <sub>5</sub>	H
776	Cl	X	CH <sub>2</sub> CH <sub>2</sub>		*	H	COCH <sub>3</sub>
777	Cl	X	CH <sub>2</sub> CH <sub>2</sub>		H	H	COCH <sub>2</sub> Cl
778	Cl	X	CH <sub>2</sub> CH <sub>2</sub>		H	H	COC <sub>4</sub> H <sub>9</sub>

SUBSTITUTE SHEET



173

Ex. #	R <sup>1</sup>	R <sup>2</sup>	A	L	B E	P
779	Cl	X	CH <sub>2</sub> CH <sub>2</sub>		H CH <sub>3</sub>	COCH <sub>3</sub>
780	Cl	X	CH <sub>2</sub> CH <sub>2</sub>		H C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
781	Cl	X	CH <sub>2</sub> CH <sub>2</sub>		* H	H
782	Cl	X	CH <sub>2</sub> CH <sub>2</sub>		H CH <sub>3</sub>	H
783	Cl	X	CH <sub>2</sub> CH <sub>2</sub>		H C <sub>2</sub> H <sub>5</sub>	H
784	Cl	X	C <sub>3</sub> H <sub>6</sub> (n)	-NH-	H H	COCH <sub>3</sub>
785	Cl	X	C <sub>3</sub> H <sub>6</sub> (n)	-NH-	H H	COCH <sub>2</sub> Cl
786	Cl	X	C <sub>3</sub> H <sub>6</sub> (n)	-NH-	H H	COC <sub>4</sub> H <sub>9</sub>



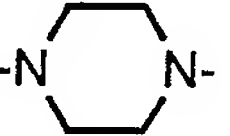
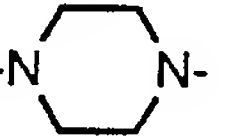
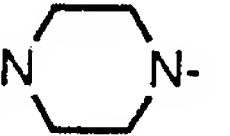
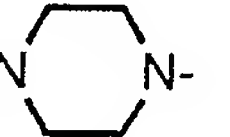
SUBSTITUTE SHEET

174

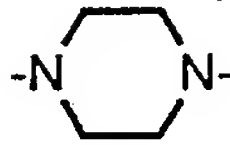
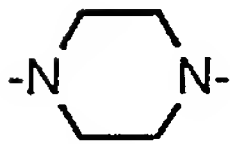
Ex. #	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
787	Cl	X	C <sub>3</sub> H <sub>6</sub> (n)	-NH-	H	CH <sub>3</sub>	COCH <sub>3</sub>
788	Cl	X	C <sub>3</sub> H <sub>6</sub> (n)	-NH-	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
789	Cl	X	C <sub>3</sub> H <sub>6</sub> (n)	-NH-	H	H	H
790	Cl	X	C <sub>3</sub> H <sub>6</sub> (n)	-NH-	H	CH <sub>3</sub>	H
791	Cl	X	C <sub>3</sub> H <sub>6</sub> (n)	-NH-	H	C <sub>2</sub> H <sub>5</sub>	H
792	Cl	X	C <sub>3</sub> H <sub>6</sub> (n)	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>3</sub>
793	Cl	X	C <sub>3</sub> H <sub>6</sub> (n)	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>2</sub> Cl
794	Cl	X	C <sub>3</sub> H <sub>6</sub> (n)	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COC <sub>4</sub> H <sub>9</sub>
795	Cl	X	C <sub>3</sub> H <sub>6</sub> (n)	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	CH <sub>3</sub>	COCH <sub>3</sub>
796	Cl	X	C <sub>3</sub> H <sub>6</sub> (n)	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
797	Cl	X	C <sub>3</sub> H <sub>6</sub> (n)	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	H

SUBSTITUTE SHEET

175


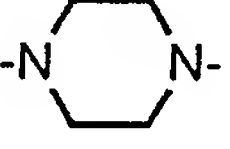
Ex. #	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
798	Cl	X	C <sub>3</sub> H <sub>6</sub> (n)	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	CH <sub>3</sub>	H
799	Cl	X	C <sub>3</sub> H <sub>6</sub> (n)	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	C <sub>2</sub> H <sub>5</sub>	H
800	Cl	X	C <sub>3</sub> H <sub>6</sub> (n)		*	H	COCH <sub>3</sub>
801	Cl	X	C <sub>3</sub> H <sub>6</sub> (n)		H	H	COCH <sub>2</sub> Cl
802	Cl	X	C <sub>3</sub> H <sub>6</sub> (n)		H	H	COC <sub>4</sub> H <sub>9</sub>
803	Cl	X	C <sub>3</sub> H <sub>6</sub> (n)		H	CH <sub>3</sub>	COCH <sub>3</sub>
804	Cl	X	C <sub>3</sub> H <sub>6</sub> (n)		H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
805	Cl	X	C <sub>3</sub> H <sub>6</sub> (n)		*	H	H

SUBSTITUTE SHEET



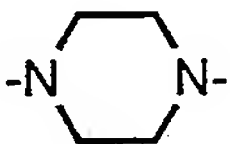
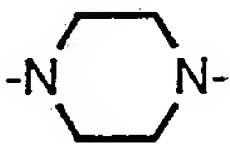
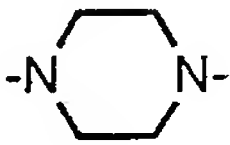
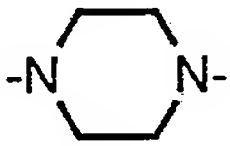

Ex. #	R <sup>1</sup>	R <sup>2</sup>	A	L	B E	P
806	Cl	X	C <sub>3</sub> H <sub>6</sub> (n)		H CH <sub>3</sub>	H
807	Cl	X	C <sub>3</sub> H <sub>6</sub> (n)		H C <sub>2</sub> H <sub>5</sub>	H
808	Cl	X	C <sub>4</sub> H <sub>8</sub> (n)	-NH-	H H	COCH <sub>3</sub>
809	Cl	X	C <sub>4</sub> H <sub>8</sub> (n)	-NH-	H H	COCH <sub>2</sub> Cl
810	Cl	X	C <sub>4</sub> H <sub>8</sub> (n)	-NH-	H H	COC <sub>4</sub> H <sub>9</sub>
811	Cl	X	C <sub>4</sub> H <sub>8</sub> (n)	-NH-	H CH <sub>3</sub>	COCH <sub>3</sub>
812	Cl	X	C <sub>4</sub> H <sub>8</sub> (n)	-NH-	H C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
813	Cl	X	C <sub>4</sub> H <sub>8</sub> (n)	-NH-	H H	H
814	Cl	X	C <sub>4</sub> H <sub>8</sub> (n)	-NH-	H CH <sub>3</sub>	H
815	Cl	X	C <sub>4</sub> H <sub>8</sub> (n)	-NH-	H C <sub>2</sub> H <sub>5</sub>	H
816	Cl	X	C <sub>4</sub> H <sub>8</sub> (n)	-NHCH <sub>2</sub> CH <sub>2</sub> -	H H	COCH <sub>3</sub>

SUBSTITUTE SHEET








177




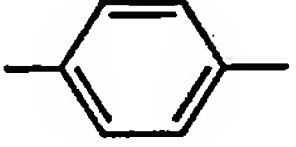



Ex. #	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
817	Cl	X	C <sub>4</sub> H <sub>8</sub> (n)	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>2</sub> Cl
818	Cl	X	C <sub>4</sub> H <sub>8</sub> (n)	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COC <sub>4</sub> H <sub>9</sub>
819	Cl	X	C <sub>4</sub> H <sub>8</sub> (n)	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	CH <sub>3</sub>	COCH <sub>3</sub>
820	Cl	X	C <sub>4</sub> H <sub>8</sub> (n)	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
821	Cl	X	C <sub>4</sub> H <sub>8</sub> (n)	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	H
822	Cl	X	C <sub>4</sub> H <sub>8</sub> (n)	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	CH <sub>3</sub>	H
823	Cl	X	C <sub>4</sub> H <sub>8</sub> (n)	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	C <sub>2</sub> H <sub>5</sub>	H
824	Cl	X	C <sub>4</sub> H <sub>8</sub> (n)		*	H	COCH <sub>3</sub>
825	Cl	X	C <sub>4</sub> H <sub>8</sub> (n)		H	H	COCH <sub>2</sub> Cl

SUBSTITUTE SHEET

Ex. #	R <sup>1</sup>	R <sup>2</sup>	A	L	B E	P
826	Cl	X	C <sub>4</sub> H <sub>8</sub> (n)		H H	COC <sub>4</sub> H <sub>9</sub>
827	Cl	X	C <sub>4</sub> H <sub>8</sub> (n)		H CH <sub>3</sub>	COCH <sub>3</sub>
828	Cl	X	C <sub>4</sub> H <sub>8</sub> (n)		H C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
829	Cl	X	C <sub>4</sub> H <sub>8</sub> (n)		* H	H
830	Cl	X	C <sub>4</sub> H <sub>8</sub> (n)		H CH <sub>3</sub>	H
831	Cl	X	C <sub>4</sub> H <sub>8</sub> (n)		H C <sub>2</sub> H <sub>5</sub>	H
832	Cl	X		-NH-	H H	COCH <sub>3</sub>



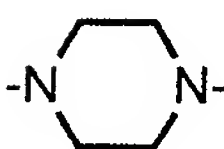
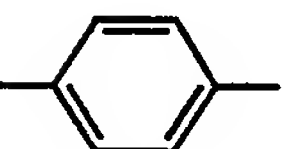
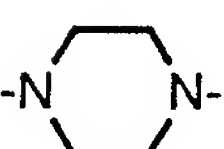
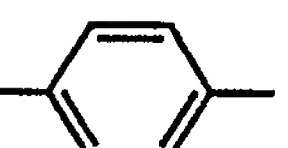

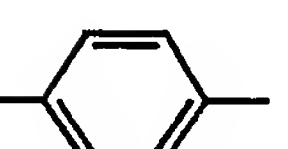
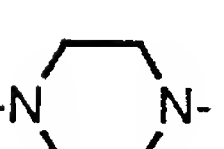
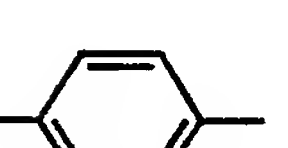
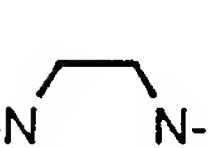
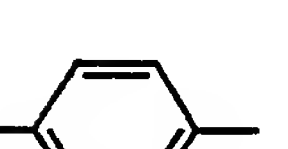
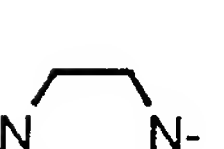
SUBSTITUTE SHEET


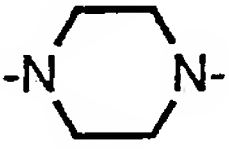

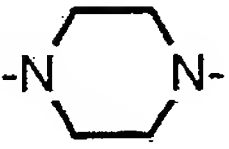
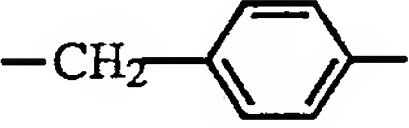
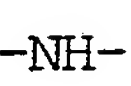
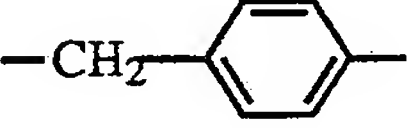

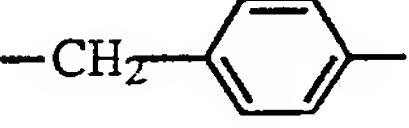
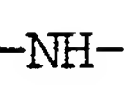
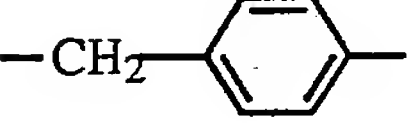
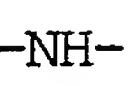
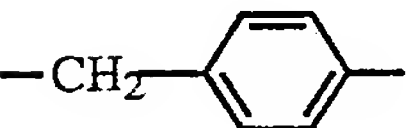

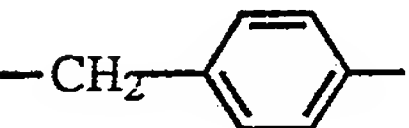

Ex. #	R <sup>1</sup>	R <sup>2</sup>	A	L	B E	P
833	Cl	X		-NH-	H H	COCH <sub>2</sub> Cl
834	Cl	X		-NH-	H H	COC <sub>4</sub> H <sub>9</sub>
835	Cl	X		-NH-	H CH <sub>3</sub>	COCH <sub>3</sub>
836	Cl	X		-NH-	H C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
837	Cl	X		-NH-	H H	H
838	Cl	X		-NH-	H CH <sub>3</sub>	H
839	Cl	X		-NH-	H C <sub>2</sub> H <sub>5</sub>	H

Ex. #	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
840	Cl	X		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>3</sub>
841	Cl	X		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>2</sub> Cl
842	Cl	X		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COC <sub>4</sub> H <sub>9</sub>
843	Cl	X		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	CH <sub>3</sub>	COCH <sub>3</sub>
844	Cl	X		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
845	Cl	X		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	H
846	Cl	X		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	CH <sub>3</sub>	H

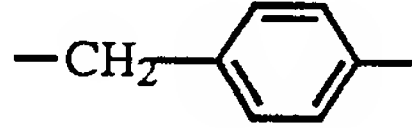
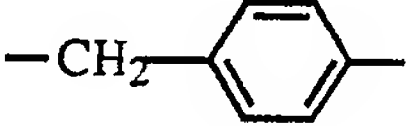
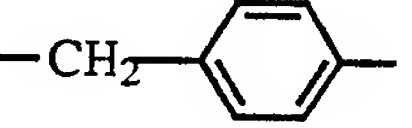
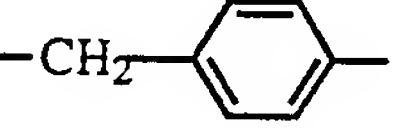
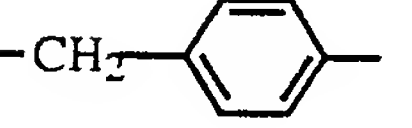
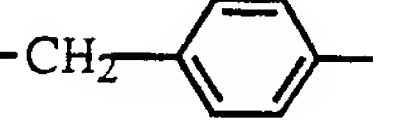
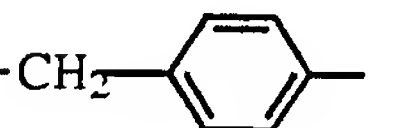
SUBSTITUTE SHEET

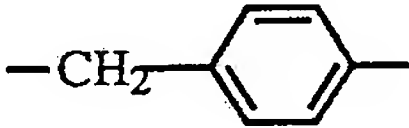
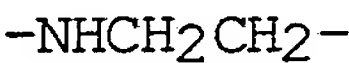
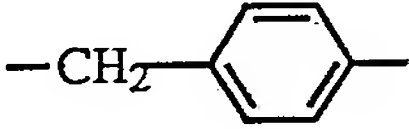
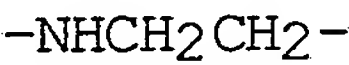
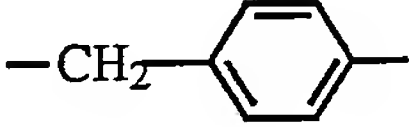
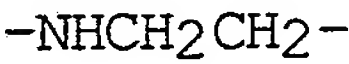
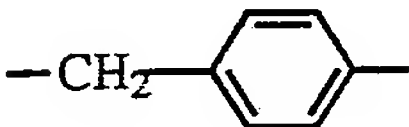

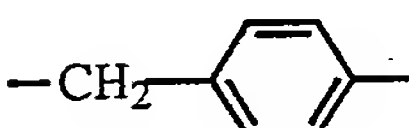

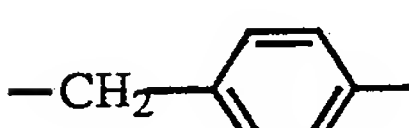
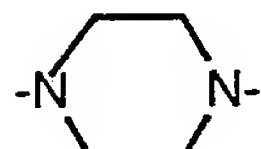
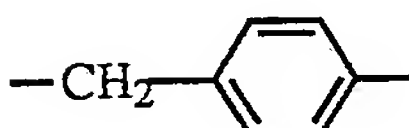
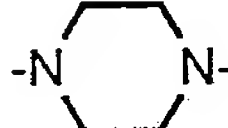


Ex. #	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
847	Cl	X		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	C <sub>2</sub> H <sub>5</sub>	H
848	Cl	X			*	H	COCH <sub>3</sub>
849	Cl	X			H	H	COCH <sub>2</sub> Cl
850	Cl	X			H	H	COC <sub>4</sub> H <sub>9</sub>
851	Cl	X			H	CH <sub>3</sub>	COCH <sub>3</sub>
852	Cl	X			H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
853	Cl	X			*	H	H

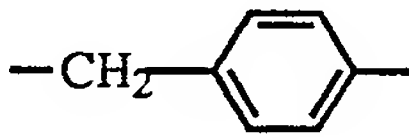

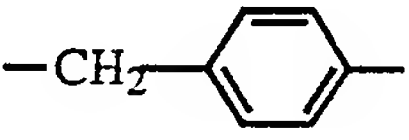

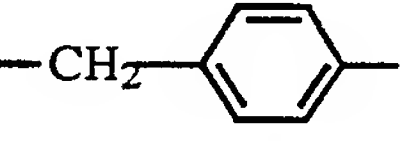
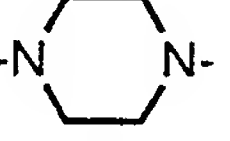
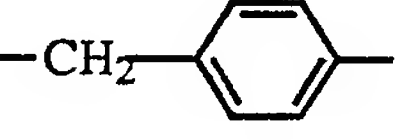
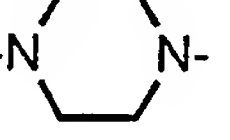
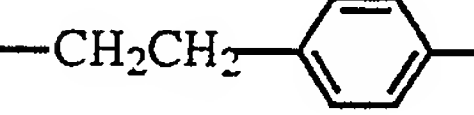
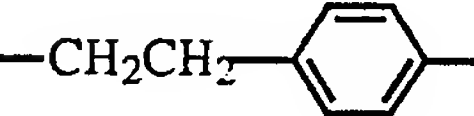
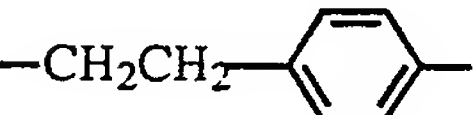
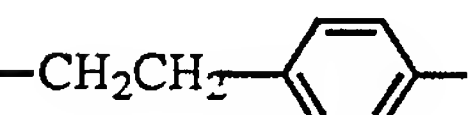
Ex. #	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
854	Cl	X			H	CH <sub>3</sub>	H
855	Cl	X			H	C <sub>2</sub> H <sub>5</sub>	H
856	Cl	X			H	H	COCH <sub>3</sub>
857	Cl	X			H	H	COCH <sub>2</sub> Cl
858	Cl	X			H	H	COC <sub>4</sub> H <sub>9</sub>
859	Cl	X			H	CH <sub>3</sub>	COCH <sub>3</sub>
860	Cl	X			H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
861	Cl	X			H	H	H

SUBSTITUTE SHEET

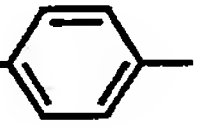
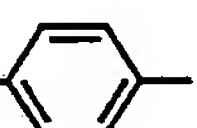
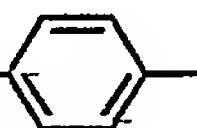
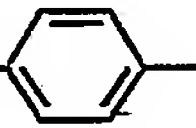
Ex. #	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
862	Cl	X		-NH-	H	CH <sub>3</sub>	H
863	Cl	X		-NH-	H	C <sub>2</sub> H <sub>5</sub>	H
864	Cl	X		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>3</sub>
865	Cl	X		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>2</sub> Cl
866	Cl	X		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COC <sub>4</sub> H <sub>9</sub>
867	Cl	X		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	CH <sub>3</sub>	COCH <sub>3</sub>
868	Cl	X		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>

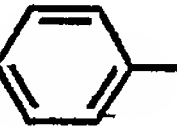

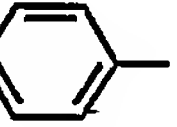
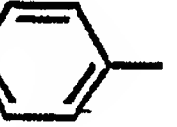
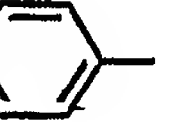
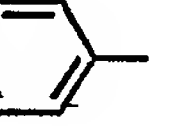
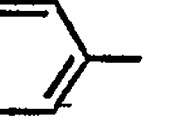
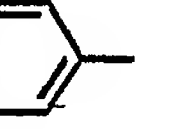
Ex. #	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
869	Cl	X			H	H	H
870	Cl	X			H	CH <sub>3</sub>	H
871	Cl	X			H	C <sub>2</sub> H <sub>5</sub>	H
872	Cl	X			*	H	COCH <sub>3</sub>
873	Cl	X			H	H	COCH <sub>2</sub> Cl
874	Cl	X			H	H	COC <sub>4</sub> H <sub>9</sub>
875	Cl	X			H	CH <sub>3</sub>	COCH <sub>3</sub>

SUBSTITUTE SHEET

Ex. #	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
876	Cl	X			H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
877	Cl	X			*	H	H
878	Cl	X			H	CH <sub>3</sub>	H
879	Cl	X			H	C <sub>2</sub> H <sub>5</sub>	H
880	Cl	X		-NH-	H	H	COCH <sub>3</sub>
881	Cl	X		-NH-	H	H	COCH <sub>2</sub> Cl
882	Cl	X		-NH-	H	H	COC <sub>4</sub> H <sub>9</sub>
883	Cl	X		-NH-	H	CH <sub>3</sub>	COCH <sub>3</sub>

SUBSTITUTE SHEET

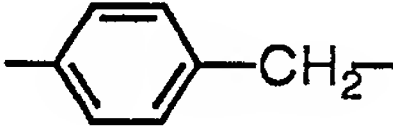
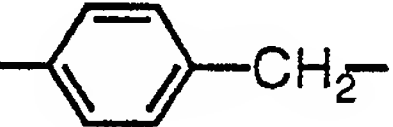
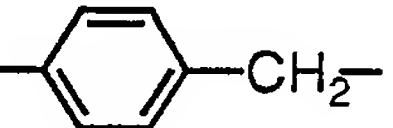
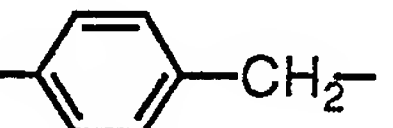
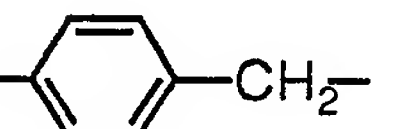
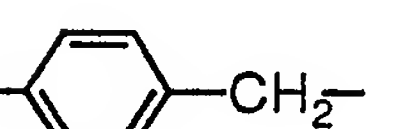
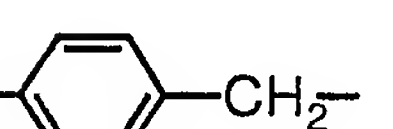
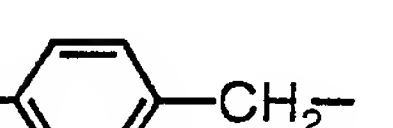
Ex. #	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
884	Cl	X	$-\text{CH}_2\text{CH}_2-$ 	$-\text{NH}-$	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
885	Cl	X	$-\text{CH}_2\text{CH}_2-$ 	$-\text{NH}-$	H	H	H
886	Cl	X	$-\text{CH}_2\text{CH}_2-$ 	$-\text{NH}-$	H	CH <sub>3</sub>	H
887	Cl	X	$-\text{CH}_2\text{CH}_2-$ 	$-\text{NH}-$	H	C <sub>2</sub> H <sub>5</sub>	H

Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
888	Cl	X	$\text{---CH}_2\text{CH}_2\text{---}$ 	$\text{---NHCH}_2\text{CH}_2\text{---}$	H	H	$\text{COCH}_3$
889	Cl	X	$\text{---CH}_2\text{CH}_2\text{---}$ 	$\text{---NHCH}_2\text{CH}_2\text{---}$	H	H	$\text{COCH}_2\text{Cl}$
890	Cl	X	$\text{---CH}_2\text{CH}_2\text{---}$ 	$\text{---NHCH}_2\text{CH}_2\text{---}$	H	H	$\text{COC}_4\text{H}_9$
891	Cl	X	$\text{---CH}_2\text{CH}_2\text{---}$ 	$\text{---NHCH}_2\text{CH}_2\text{---}$	H	$\text{CH}_3$	$\text{COCH}_3$
892	Cl	X	$\text{---CH}_2\text{CH}_2\text{---}$ 	$\text{---NHCH}_2\text{CH}_2\text{---}$	H	$\text{C}_2\text{H}_5$	$\text{COCH}_3$
893	Cl	X	$\text{---CH}_2\text{CH}_2\text{---}$ 	$\text{---NHCH}_2\text{CH}_2\text{---}$	H	H	H
894	Cl	X	$\text{---CH}_2\text{CH}_2\text{---}$ 	$\text{---NHCH}_2\text{CH}_2\text{---}$	H	$\text{CH}_3$	H
895	Cl	X	$\text{---CH}_2\text{CH}_2\text{---}$ 	$\text{---NHCH}_2\text{CH}_2\text{---}$	H	$\text{C}_2\text{H}_5$	H

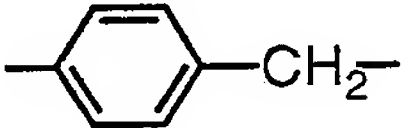
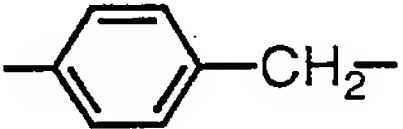
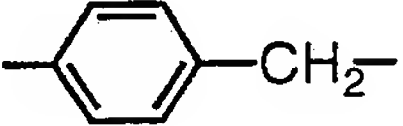
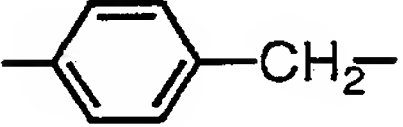
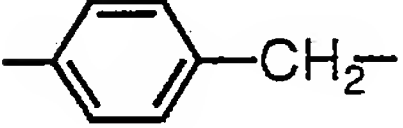
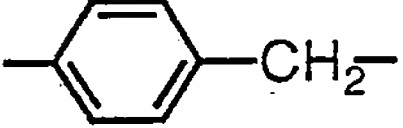
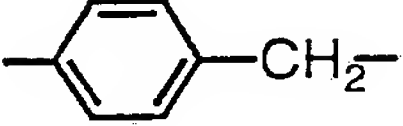
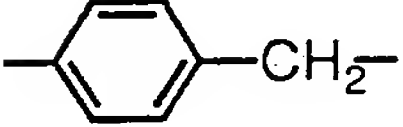
Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
896	Cl	X			*	H	COCH <sub>3</sub>
897	Cl	X			H	H	COCH <sub>2</sub> Cl
898	Cl	X			H	H	COC <sub>4</sub> H <sub>9</sub>
899	Cl	X			H	CH <sub>3</sub>	COCH <sub>3</sub>
900	Cl	X			H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
901	Cl	X			*	H	H
902	Cl	X			H	CH <sub>3</sub>	H
903	Cl	X			H	C <sub>2</sub> H <sub>5</sub>	H

SUBSTITUTE SHEET

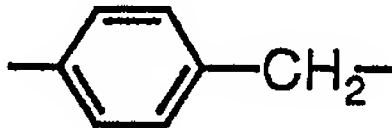
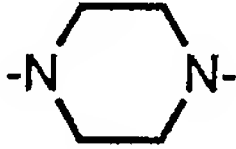
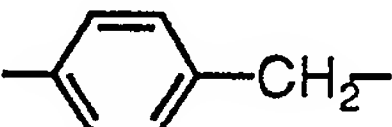
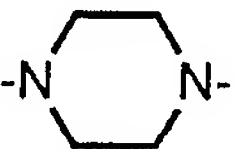
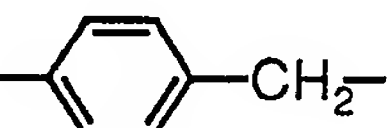
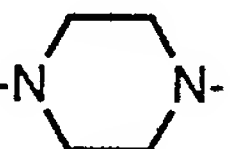
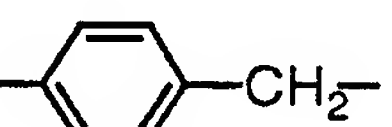
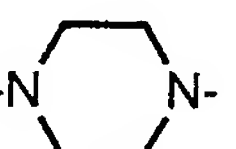
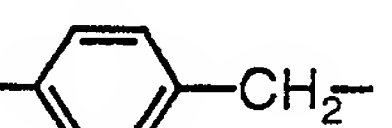
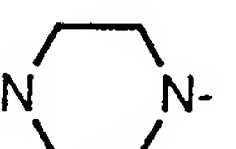
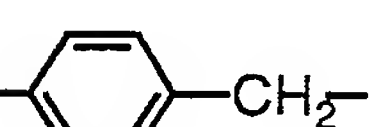
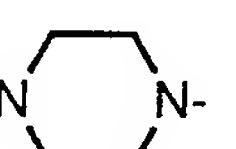
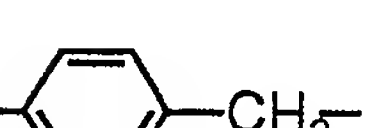
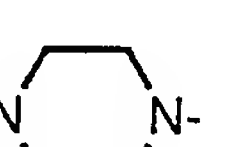


Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
904	Cl	X		-NH-	H	H	COCH <sub>3</sub>
905	Cl	X		-NH-	H	H	COCH <sub>2</sub> Cl
906	Cl	X		-NH-	H	H	COC <sub>4</sub> H <sub>9</sub>
907	Cl	X		-NH-	H	CH <sub>3</sub>	COCH <sub>3</sub>
908	Cl	X		-NH-	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
909	Cl	X		-NH-	H	H	H
910	Cl	X		-NH-	H	CH <sub>3</sub>	H
911	Cl	X		-NH-	H	C <sub>2</sub> H <sub>5</sub>	H

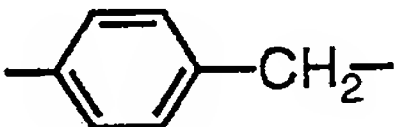
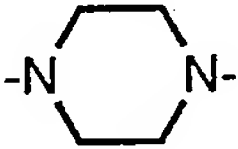
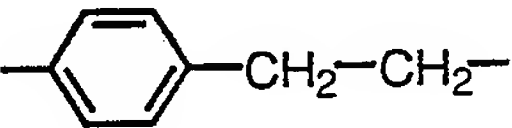
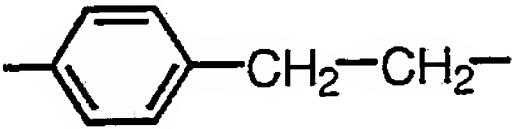
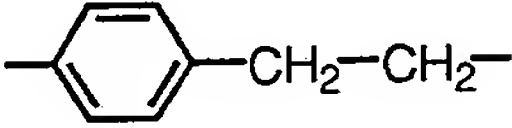
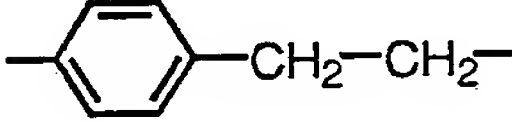
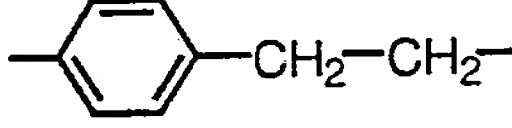
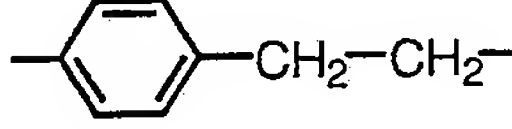
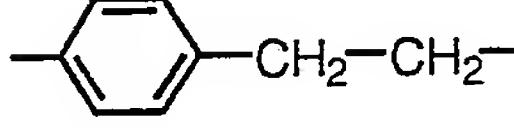
SUBSTITUTE SHEET

Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
912	Cl	X		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>3</sub>
913	Cl	X		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>2</sub> Cl
914	Cl	X		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COC <sub>4</sub> H <sub>9</sub>
915	Cl	X		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	CH <sub>3</sub>	COCH <sub>3</sub>
916	Cl	X		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
917	Cl	X		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	H
918	Cl	X		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	CH <sub>3</sub>	H
919	Cl	X		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	C <sub>2</sub> H <sub>5</sub>	H

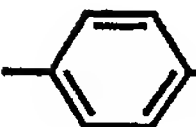
SUBSTITUTE SHEET

Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
920	Cl	X			*	H	COCH <sub>3</sub>
921	Cl	X			H	H	COCH <sub>2</sub> Cl
922	Cl	X			H	H	COC <sub>4</sub> H <sub>9</sub>
923	Cl	X			H	CH <sub>3</sub>	COCH <sub>3</sub>
924	Cl	X			H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
925	Cl	X			*	H	H
926	Cl	X			H	CH <sub>3</sub>	H

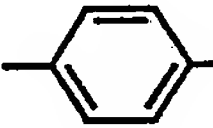

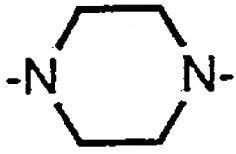
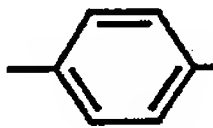

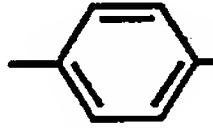

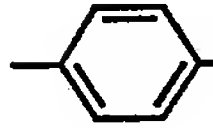

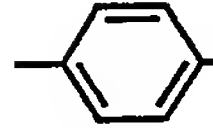
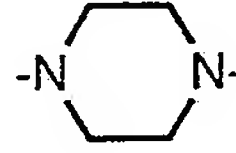
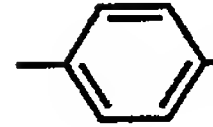
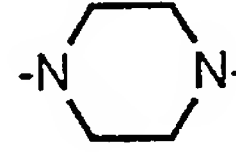
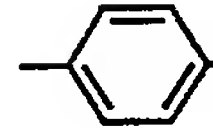
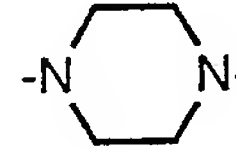
SUBSTITUTE SHEET

Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
927	Cl	X			H	C <sub>2</sub> H <sub>5</sub>	H
928	Cl	X		-NH-	H	H	COCH <sub>3</sub>
929	Cl	X		-NH-	H	H	COCH <sub>2</sub> Cl
930	Cl	X		-NH-	H	H	COC <sub>4</sub> H <sub>9</sub>
931	Cl	X		-NH-	H	CH <sub>3</sub>	COCH <sub>3</sub>
932	Cl	X		-NH-	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
933	Cl	X		-NH-	H	H	H
934	Cl	X		-NH-	H	CH <sub>3</sub>	H

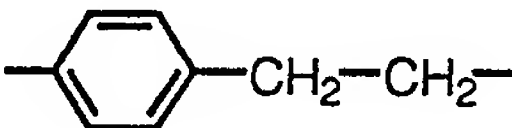




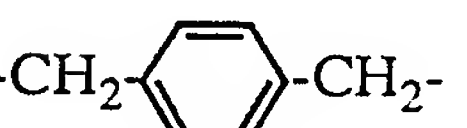
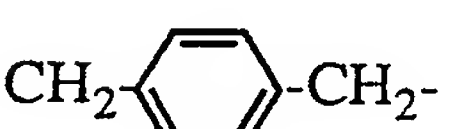


SUBSTITUTE SHEET

Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
935	Cl	X	 -CH <sub>2</sub> -CH <sub>2</sub> -	-NH-	H	C <sub>2</sub> H <sub>5</sub>	H
936	Cl	X	 -CH <sub>2</sub> -CH <sub>2</sub> -	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>3</sub>
937	Cl	X	 -CH <sub>2</sub> -CH <sub>2</sub> -	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>2</sub> Cl
938	Cl	X	 -CH <sub>2</sub> -CH <sub>2</sub> -	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COC <sub>4</sub> H <sub>9</sub>
939	Cl	X	 -CH <sub>2</sub> -CH <sub>2</sub> -	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	CH <sub>3</sub>	COCH <sub>3</sub>
940	Cl	X	 -CH <sub>2</sub> -CH <sub>2</sub> -	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
941	Cl	X	 -CH <sub>2</sub> -CH <sub>2</sub> -	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	H
942	Cl	X	 -CH <sub>2</sub> -CH <sub>2</sub> -	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	CH <sub>3</sub>	H

SUBSTITUTE SHEET

Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
943	Cl	X	 -CH <sub>2</sub> -CH <sub>2</sub> -	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	C <sub>2</sub> H <sub>5</sub>	H
944	Cl	X	 -CH <sub>2</sub> -CH <sub>2</sub> -		*	H	COCH <sub>3</sub>
945	Cl	X	 -CH <sub>2</sub> -CH <sub>2</sub> -		H	H	COCH <sub>2</sub> Cl
946	Cl	X	 -CH <sub>2</sub> -CH <sub>2</sub> -		H	H	COC <sub>4</sub> H <sub>9</sub>
947	Cl	X	 -CH <sub>2</sub> -CH <sub>2</sub> -		H	CH <sub>3</sub>	COCH <sub>3</sub>
948	Cl	X	 -CH <sub>2</sub> -CH <sub>2</sub> -		H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
949	Cl	X	 -CH <sub>2</sub> -CH <sub>2</sub> -		*	H	H
950	Cl	X	 -CH <sub>2</sub> -CH <sub>2</sub> -		H	CH <sub>3</sub>	H

SUBSTITUTE SHEET


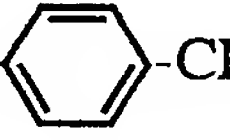


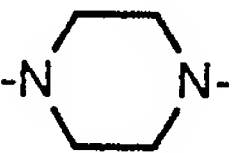
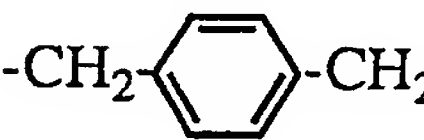

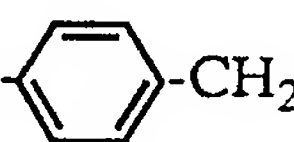
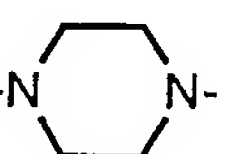
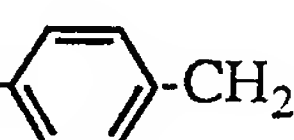
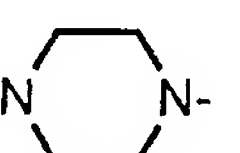
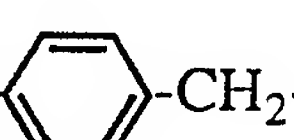
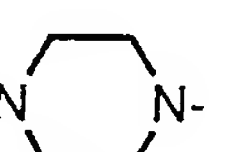
Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
951	Cl	X			H	C <sub>2</sub> H <sub>5</sub>	H
952	Cl	X		-NH-	H	H	COCH <sub>3</sub>
953	Cl	X		-NH-	H	H	COCH <sub>2</sub> Cl
954	Cl	X		-NH-	H	H	COC <sub>4</sub> H <sub>9</sub>
955	Cl	X		-NH-	H	CH <sub>3</sub>	COCH <sub>3</sub>
956	Cl	X		-NH-	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
957	Cl	X		-NH-	H	H	H
958	Cl	X		-NH-	H	CH <sub>3</sub>	H

SUBSTITUTE SHEET





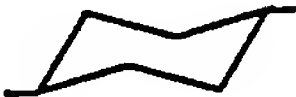






Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
959	Cl	X	$-\text{CH}_2-\text{C}_6\text{H}_4-\text{CH}_2-$	$-\text{NH}-$	H	C <sub>2</sub> H <sub>5</sub>	H
960	Cl	X	$-\text{CH}_2-\text{C}_6\text{H}_4-\text{CH}_2-$	$-\text{NHCH}_2\text{CH}_2-$	H	H	COCH <sub>3</sub>
961	Cl	X	$-\text{CH}_2-\text{C}_6\text{H}_4-\text{CH}_2-$	$-\text{NHCH}_2\text{CH}_2-$	H	H	COCH <sub>2</sub> Cl
962	Cl	X	$-\text{CH}_2-\text{C}_6\text{H}_4-\text{CH}_2-$	$-\text{NHCH}_2\text{CH}_2-$	H	H	COC <sub>4</sub> H <sub>9</sub>
963	Cl	X	$-\text{CH}_2-\text{C}_6\text{H}_4-\text{CH}_2-$	$-\text{NHCH}_2\text{CH}_2-$	H	CH <sub>3</sub>	COCH <sub>3</sub>
964	Cl	X	$-\text{CH}_2-\text{C}_6\text{H}_4-\text{CH}_2-$	$-\text{NHCH}_2\text{CH}_2-$	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
965	Cl	X	$-\text{CH}_2-\text{C}_6\text{H}_4-\text{CH}_2-$	$-\text{NHCH}_2\text{CH}_2-$	H	H	H
966	Cl	X	$-\text{CH}_2-\text{C}_6\text{H}_4-\text{CH}_2-$	$-\text{NHCH}_2\text{CH}_2-$	H	CH <sub>3</sub>	H

SUBSTITUTE SHEET

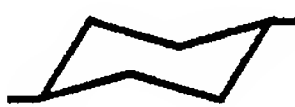
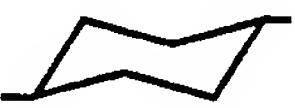
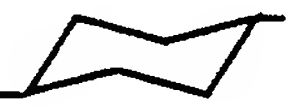







Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
967	Cl	X		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	C <sub>2</sub> H <sub>5</sub>	H
968	Cl	X			*	H	COCH <sub>3</sub>
969	Cl	X			H	H	COCH <sub>2</sub> Cl
970	Cl	X			H	H	COC <sub>4</sub> H <sub>9</sub>
971	Cl	X			H	CH <sub>3</sub>	COCH <sub>3</sub>
972	Cl	X			H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
973	Cl	X			*	H	H

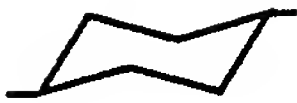


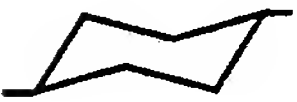
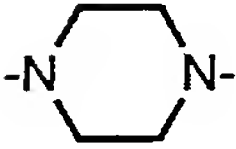
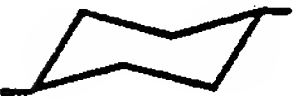
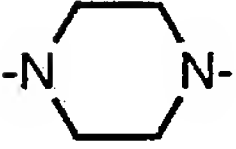


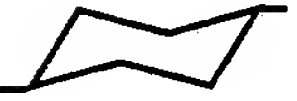

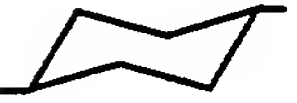



SUBSTITUTE SHEET

Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
974	Cl	X			H	CH <sub>3</sub>	H
975	Cl	X			H	C <sub>2</sub> H <sub>5</sub>	H
976	Cl	X		-NH-	H	H	COCH <sub>3</sub>
977	Cl	X		-NH-	H	H	COCH <sub>2</sub> Cl
978	Cl	X		-NH-	H	H	COC <sub>4</sub> H <sub>9</sub>
979	Cl	X		-NH-	H	CH <sub>3</sub>	COCH <sub>3</sub>
980	Cl	X		-NH-	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
981	Cl	X		-NH-	H	H	H
982	Cl	X		-NH-	H	CH <sub>3</sub>	H


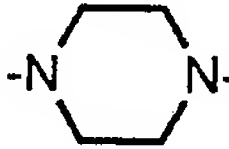







SUBSTITUTE SHEET

Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
983	Cl	X		-NH-	H	C <sub>2</sub> H <sub>5</sub>	H
984	Cl	X		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>3</sub>
985	Cl	X		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>2</sub> Cl
986	Cl	X		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COC <sub>4</sub> H <sub>9</sub>
987	Cl	X		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	CH <sub>3</sub>	COCH <sub>3</sub>
988	Cl	X		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
989	Cl	X		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	H
990	Cl	X		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	CH <sub>3</sub>	H









SUBSTITUTE SHEET





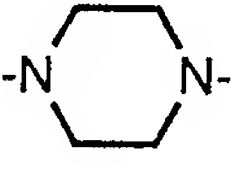

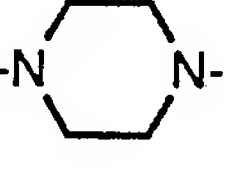

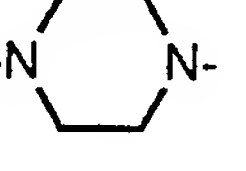

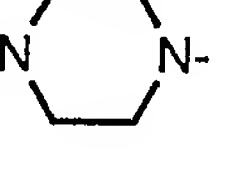

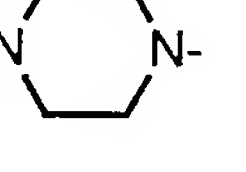

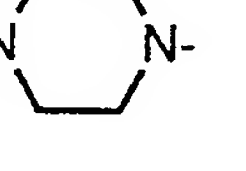
Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
991	Cl	X		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	C <sub>2</sub> H <sub>5</sub>	H
992	Cl	X			*	H	COCH <sub>3</sub>
993	Cl	X			H	H	COCH <sub>2</sub> Cl
994	Cl	X			H	H	COC <sub>4</sub> H <sub>9</sub>
995	Cl	X			H	CH <sub>3</sub>	COCH <sub>3</sub>
996	Cl	X			H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
997	Cl	X			*	H	H
998	Cl	X			H	CH <sub>3</sub>	H

SUBSTITUTE SHEET


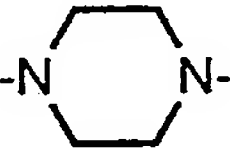
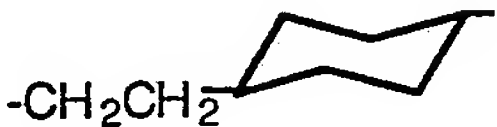
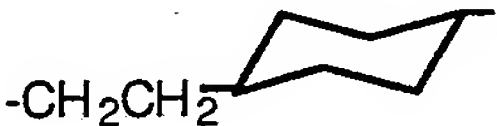
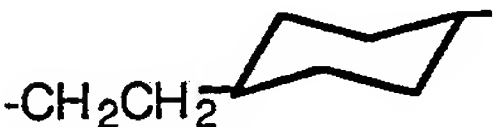
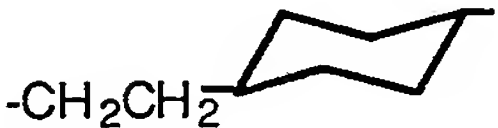
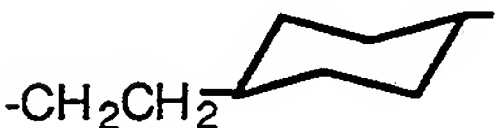
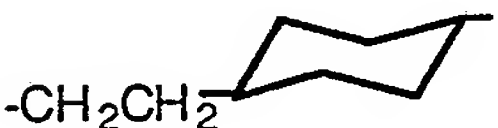
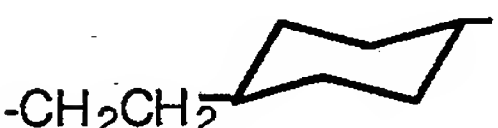
Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
999	Cl	X			H	C <sub>2</sub> H <sub>5</sub>	H
1000		Cl		X			-NH- H
1001		Cl		X			-NH- H
1002	Cl	X		-NH-	H H		COC <sub>4</sub> H <sub>9</sub>
1003	Cl	X		-NH-	H CH <sub>3</sub>		COCH <sub>3</sub>
1004	Cl	X		-NH-	H C <sub>2</sub> H <sub>5</sub>		COCH <sub>3</sub>
1005	Cl	X		-NH-	H H		H
1006	Cl	X		-NH-	H CH <sub>3</sub>		H

SUBSTITUTE SHEET

Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1007	Cl	X	-CH <sub>2</sub> - 	-NH-	H	C <sub>2</sub> H <sub>5</sub>	H
1008	Cl	X	-CH <sub>2</sub> - 	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>3</sub>
1009	Cl	X	-CH <sub>2</sub> - 	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>2</sub> Cl
1010	Cl	X	-CH <sub>2</sub> - 	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COC <sub>4</sub> H <sub>9</sub>
1011	Cl	X	-CH <sub>2</sub> - 	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	CH <sub>3</sub>	COCH <sub>3</sub>
1012	Cl	X	-CH <sub>2</sub> - 	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
1013	Cl	X	-CH <sub>2</sub> - 	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	H
1014	Cl	X	-CH <sub>2</sub> - 	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	CH <sub>3</sub>	H










Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1015	Cl	X	-CH <sub>2</sub> - 	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	C <sub>2</sub> H <sub>5</sub>	H
1016	Cl	X	-CH <sub>2</sub> - 	-N  -	*	H	COCH <sub>3</sub>
1017	Cl	X	-CH <sub>2</sub> - 	-N  -	H	H	COCH <sub>2</sub> Cl
1018	Cl	X	-CH <sub>2</sub> - 	-N  -	H	H	COC <sub>4</sub> H <sub>9</sub>
1019	Cl	X	-CH <sub>2</sub> - 	-N  -	H	CH <sub>3</sub>	COCH <sub>3</sub>
1020	Cl	X	-CH <sub>2</sub> - 	-N  -	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
1021	Cl	X	-CH <sub>2</sub> - 	-N  -	*	H	H
1022	Cl	X	-CH <sub>2</sub> - 	-N  -	H	CH <sub>3</sub>	H

SUBSTITUTE SHEET


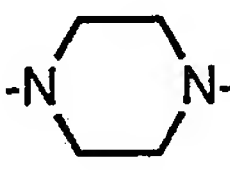

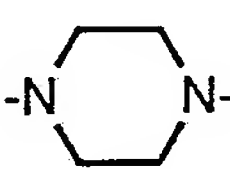

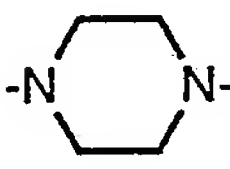

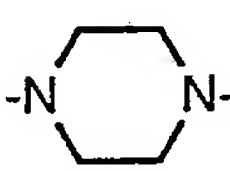

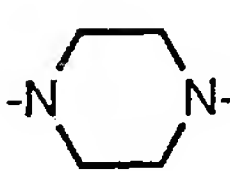
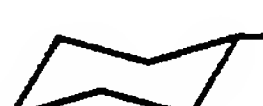
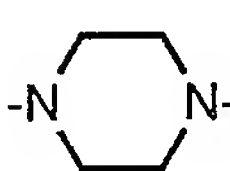

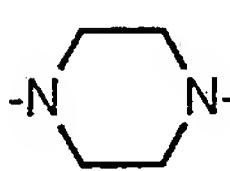

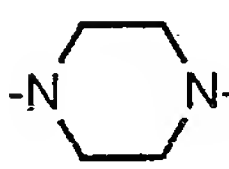
Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1023	Cl	X			H	C <sub>2</sub> H <sub>5</sub>	H
1024	Cl	X		-NH-	H	H	COCH <sub>3</sub>
1025	Cl	X		-NH-	H	H	COCH <sub>2</sub> Cl
1026	Cl	X		-NH-	H	H	COC <sub>4</sub> H <sub>9</sub>
1027	Cl	X		-NH-	H	CH <sub>3</sub>	COCH <sub>3</sub>
1028	Cl	X		-NH-	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
1029	Cl	X		-NH-	H	H	H
1030	Cl	X		-NH-	H	CH <sub>3</sub>	H

SUBSTITUTE SHEET





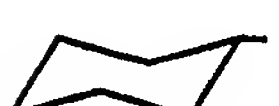





Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1031	Cl	X	-CH <sub>2</sub> CH <sub>2</sub> - 	-NH-	H	C <sub>2</sub> H <sub>5</sub>	H
1032	Cl	X	-CH <sub>2</sub> CH <sub>2</sub> - 	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>3</sub>
1033	Cl	X	-CH <sub>2</sub> CH <sub>2</sub> - 	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>2</sub> Cl
1034	Cl	X	-CH <sub>2</sub> CH <sub>2</sub> - 	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COC <sub>4</sub> H <sub>9</sub>
1035	Cl	X	-CH <sub>2</sub> CH <sub>2</sub> - 	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	CH <sub>3</sub>	COCH <sub>3</sub>
1036	Cl	X	-CH <sub>2</sub> CH <sub>2</sub> - 	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
1037	Cl	X	-CH <sub>2</sub> CH <sub>2</sub> - 	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	H
1038	Cl	X	-CH <sub>2</sub> CH <sub>2</sub> - 	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	CH <sub>3</sub>	H
1039	Cl	X	-CH <sub>2</sub> CH <sub>2</sub> - 	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	C <sub>2</sub> H <sub>5</sub>	H










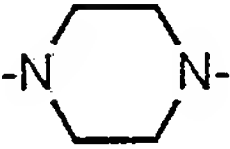
SUBSTITUTE SHEET

Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1040	Cl	X	$-\text{CH}_2\text{CH}_2-$ 		*	H	COCH <sub>3</sub>
1041	Cl	X	$-\text{CH}_2\text{CH}_2-$ 		H	H	COCH <sub>2</sub> Cl
1042	Cl	X	$-\text{CH}_2\text{CH}_2-$ 		H	H	COC <sub>4</sub> H <sub>9</sub>
1043	Cl	X	$-\text{CH}_2\text{CH}_2-$ 		H	CH <sub>3</sub>	COCH <sub>3</sub>
1044	Cl	X	$-\text{CH}_2\text{CH}_2-$ 		H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
1045	Cl	X	$-\text{CH}_2\text{CH}_2-$ 		*	H	H
1046	Cl	X	$-\text{CH}_2\text{CH}_2-$ 		H	CH <sub>3</sub>	H
1047	Cl	X	$-\text{CH}_2\text{CH}_2-$ 		H	C <sub>2</sub> H <sub>5</sub>	H

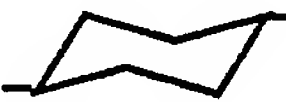




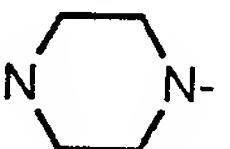

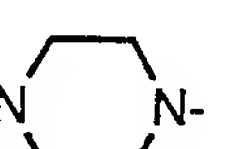

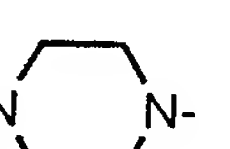

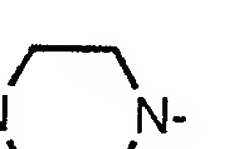

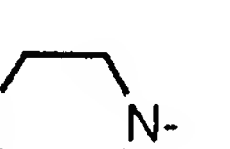

SUBSTITUTE SHEET

Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1048	Cl	X	 CH <sub>2</sub> -	-NH-	H	H	COCH <sub>3</sub>
1049	Cl	X	 CH <sub>2</sub> -	-NH-	H	H	COCH <sub>2</sub> Cl
1050	Cl	X	 CH <sub>2</sub> -	-NH-	H	H	COC <sub>4</sub> H <sub>9</sub>
1051	Cl	X	 CH <sub>2</sub> -	-NH-	H	CH <sub>3</sub>	COCH <sub>3</sub>
1052	Cl	X	 CH <sub>2</sub> -	-NH-	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
1053	Cl	X	 CH <sub>2</sub> -	-NH-	H	H	H
1054	Cl	X	 CH <sub>2</sub> -	-NH-	H	CH <sub>3</sub>	H
1055	Cl	X	 CH <sub>2</sub> -	-NH-	H	C <sub>2</sub> H <sub>5</sub>	H

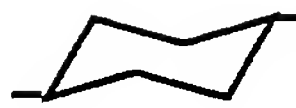
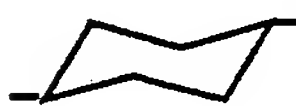







SUBSTITUTE SHEET

Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1056	Cl	X	 CH <sub>2</sub> -	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>3</sub>
1057	Cl	X	 CH <sub>2</sub> -	-NH-	H	H	COCH <sub>2</sub> Cl
1058	Cl	X	 CH <sub>2</sub> -	-NH-	H	H	COC <sub>4</sub> H <sub>9</sub>
1059	Cl	X	 CH <sub>2</sub> -	-NH-	H	CH <sub>3</sub>	COCH <sub>3</sub>
1060	Cl	X	 CH <sub>2</sub> -	-NH-	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
1061	Cl	X	 CH <sub>2</sub> -	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	H
1062	Cl	X	 CH <sub>2</sub> -	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	CH <sub>3</sub>	H
1063	Cl	X	 CH <sub>2</sub> -	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	C <sub>2</sub> H <sub>5</sub>	H
1064	Cl	X	 CH <sub>2</sub> -		*	H	COCH <sub>3</sub>


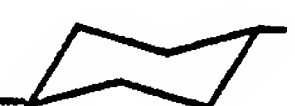





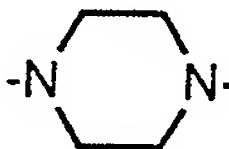


SUBSTITUTE SHEET

Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1065	Cl	X	 CH <sub>2</sub> -		H	H	COCH <sub>2</sub> Cl
1066	Cl	X	 CH <sub>2</sub> -		H	H	COC <sub>4</sub> H <sub>9</sub>
1067	Cl	X	 CH <sub>2</sub> -		H	CH <sub>3</sub>	COCH <sub>3</sub>
1068	Cl	X	 CH <sub>2</sub> -		C <sub>2</sub> H <sub>5</sub>		COC <sub>2</sub> H <sub>5</sub>
1069	Cl	X	 CH <sub>2</sub> -		*	H	H
1070	Cl	X	 CH <sub>2</sub> -		H	CH <sub>3</sub>	H
1071	Cl	X	 CH <sub>2</sub> -		H	C <sub>2</sub> H <sub>5</sub>	H
1072	Cl	X	 CH <sub>2</sub> CH <sub>2</sub> -	-NH-	H	H	COCH <sub>3</sub>

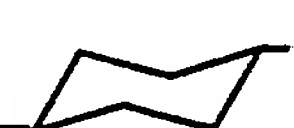
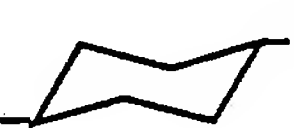
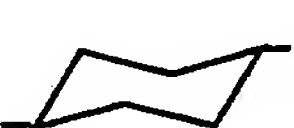
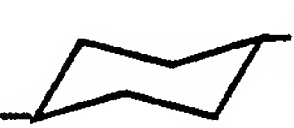
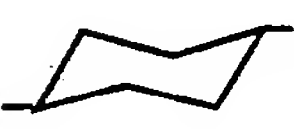
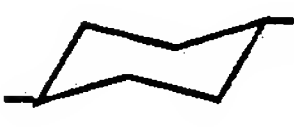
SUBSTITUTE SHEET

Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1073	Cl	X	 CH <sub>2</sub> CH <sub>2</sub> -	-NH-	H	H	COCH <sub>2</sub> Cl
1074	Cl	X	 CH <sub>2</sub> CH <sub>2</sub> -	-NH-	H	H	COC <sub>4</sub> H <sub>9</sub>
1075	Cl	X	 CH <sub>2</sub> CH <sub>2</sub> -	-NH-	H	CH <sub>3</sub>	COCH <sub>3</sub>
1076	Cl	X	 CH <sub>2</sub> CH <sub>2</sub> -	-NH-	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
1077	Cl	X	 CH <sub>2</sub> CH <sub>2</sub> -	-NH-	H	H	H
1078	Cl	X	 CH <sub>2</sub> CH <sub>2</sub> -	-NH-	H	CH <sub>3</sub>	H
1079	Cl	X	 CH <sub>2</sub> CH <sub>2</sub> -	-NH-	H	C <sub>2</sub> H <sub>5</sub>	H
1080	Cl	X	 CH <sub>2</sub> CH <sub>2</sub> -	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>3</sub>
1081	Cl	X	 CH <sub>2</sub> CH <sub>2</sub> -	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>2</sub> Cl

SUBSTITUTE SHEET


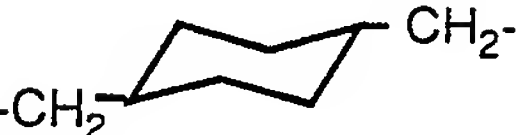






Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1082	Cl	X	 CH <sub>2</sub> CH <sub>2</sub> -	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COC <sub>4</sub> H <sub>9</sub>
1083	Cl	X	 CH <sub>2</sub> CH <sub>2</sub> -	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	CH <sub>3</sub>	COCH <sub>3</sub>
1084	Cl	X	 CH <sub>2</sub> CH <sub>2</sub> -	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
1085	Cl	X	 CH <sub>2</sub> CH <sub>2</sub> -	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	H
1086	Cl	X	 CH <sub>2</sub> CH <sub>2</sub> -	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	CH <sub>3</sub>	H
1087	Cl	X	 CH <sub>2</sub> CH <sub>2</sub> -	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	C <sub>2</sub> H <sub>5</sub>	H
1088	Cl	X	 CH <sub>2</sub> CH <sub>2</sub> -	-N  N-	*	H	COCH <sub>3</sub>
1089	Cl	X	 CH <sub>2</sub> CH <sub>2</sub> -	-N  N-	H	H	COCH <sub>2</sub> Cl

SUBSTITUTE SHEET

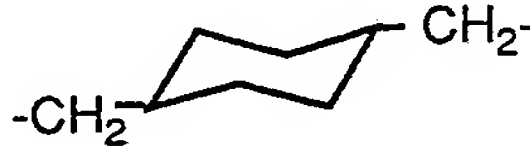
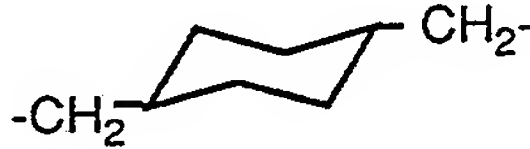
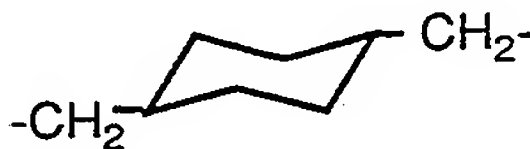
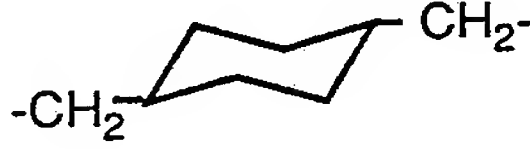
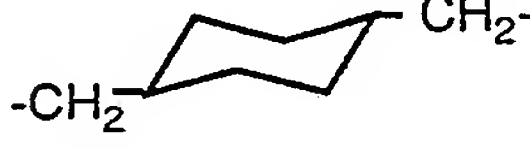
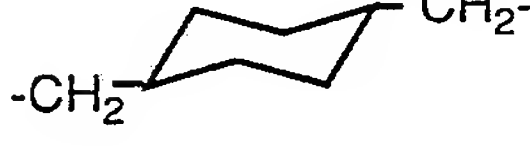
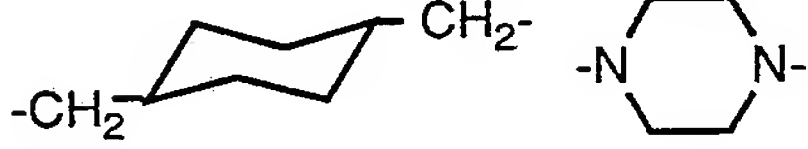
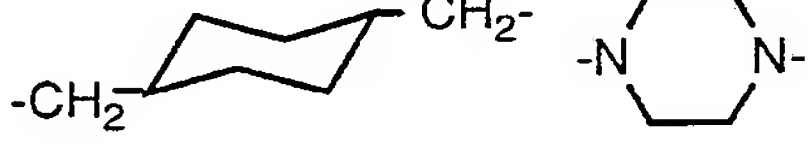
Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1090	Cl	X	 CH <sub>2</sub> CH <sub>2</sub> -	-N<img alt="piperidine ring" data-bbox="465 220 535 255"/>-	H	H	COC <sub>4</sub> H <sub>9</sub>
1091	Cl	X	 CH <sub>2</sub> CH <sub>2</sub> -	-N<img alt="piperidine ring" data-bbox="465 310 535 345"/>-	H	CH <sub>3</sub>	COCH <sub>3</sub>
1092	Cl	X	 CH <sub>2</sub> CH <sub>2</sub> -	-N<img alt="piperidine ring" data-bbox="465 400 535 435"/>-	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
1093	Cl	X	 CH <sub>2</sub> CH <sub>2</sub> -	-N<img alt="piperidine ring" data-bbox="465 490 535 525"/>-	*	H	H
1094	Cl	X	 CH <sub>2</sub> CH <sub>2</sub> -	-N<img alt="piperidine ring" data-bbox="465 580 535 615"/>-	H	CH <sub>3</sub>	H
1095	Cl	X	 CH <sub>2</sub> CH <sub>2</sub> -	-N<img alt="piperidine ring" data-bbox="465 670 535 705"/>-	H	C <sub>2</sub> H <sub>5</sub>	H
1096	Cl	X	-CH <sub>2</sub> -<img alt="Cyclohexane chair conformation with an ethyl group in the endo position" data-bbox="335 755 425 785"/>CH <sub>2</sub> -	-NH-	H	H	COCH <sub>3</sub>
1097	Cl	X	-CH <sub>2</sub> -<img alt="Cyclohexane chair conformation with an ethyl group in the endo position" data-bbox="335 845 425 875"/>CH <sub>2</sub> -	-NH-	H	H	COCH <sub>2</sub> Cl

SUBSTITUTE SHEET

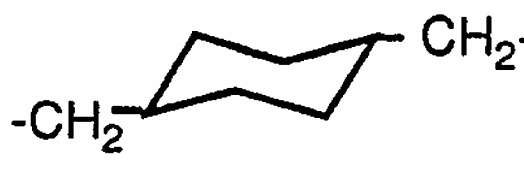
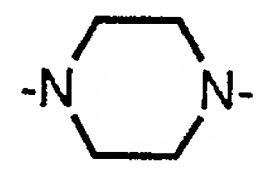
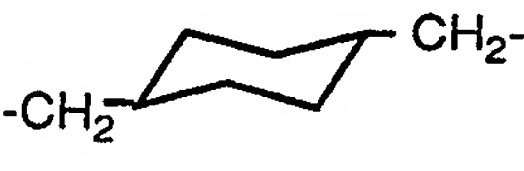
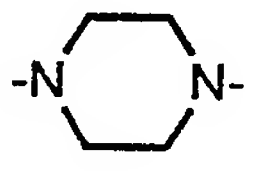

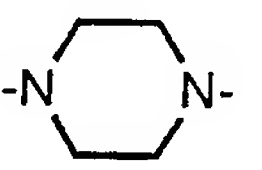

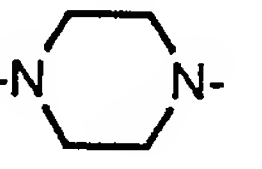

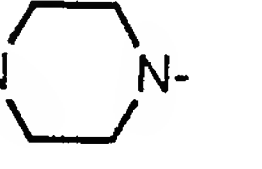

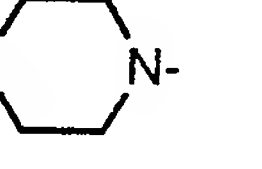


Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1098	Cl	X		-NH-	H	H	COC <sub>4</sub> H <sub>9</sub>
1099	Cl	X		-NH-	H	CH <sub>3</sub>	COCH <sub>3</sub>
1100	Cl	X		-NH-	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
1101	Cl	X		-NH-	H	H	H
1102	Cl	X		-NH-	H	CH <sub>3</sub>	H
1103	Cl	X		-NH-	H	C <sub>2</sub> H <sub>5</sub>	H
1104	Cl	X		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>3</sub>
1105	Cl	X		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>2</sub> Cl

SUBSTITUTE SHEET

Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1106	Cl	X		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COC <sub>4</sub> H <sub>9</sub>
1107	Cl	X		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	CH <sub>3</sub>	COCH <sub>3</sub>
1108	Cl	X		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
1109	Cl	X		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	H
1110	Cl	X		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	CH <sub>3</sub>	H
1111	Cl	X		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	C <sub>2</sub> H <sub>5</sub>	H
1112	Cl	X		-N-	*	H	COCH <sub>3</sub>
1113	Cl	X		-N-	H	H	COCH <sub>2</sub> Cl

SUBSTITUTE SHEET

Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1114	Cl	X			H	H	COC <sub>4</sub> H <sub>9</sub>
1115	Cl	X			H	CH <sub>3</sub>	COCH <sub>3</sub>
1116	Cl	X			H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
1117	Cl	X			*	H	H
1118	Cl	X			H	CH <sub>3</sub>	H
1119	Cl	X			H	C <sub>2</sub> H <sub>5</sub>	H
1120	X	Cl	single bond	-NH-	H	H	COCH <sub>3</sub>
1121	X	Cl	single bond	-NH-	H	H	COCH <sub>2</sub> Cl
1122	X	Cl	single bond	-NH-	H	H	COC <sub>4</sub> H <sub>9</sub>



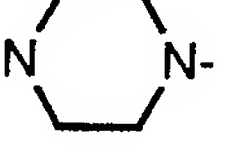
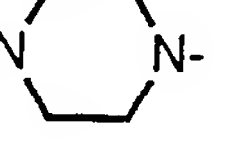
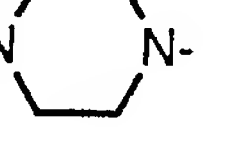
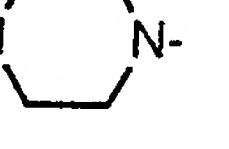
SUBSTITUTE SHEET

216


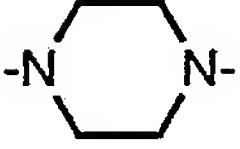
Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1123	X	Cl	single bond	-NH-	H	CH <sub>3</sub>	COCH <sub>3</sub>
1124	X	Cl	single bond	-NH-	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
1125	X	Cl	single bond	-NH-	H	H	H
1126	X	Cl	single bond	-NH-	H	CH <sub>3</sub>	H
1127	X	Cl	single bond	-NH-	H	C <sub>2</sub> H <sub>5</sub>	H
1128	X	Cl	single bond	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>3</sub>
1129	X	Cl	single bond	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>2</sub> Cl
1130	X	Cl	single bond	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COC <sub>4</sub> H <sub>9</sub>
1131	X	Cl	single bond	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	CH <sub>3</sub>	COCH <sub>3</sub>
1132	X	Cl	single bond	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
1133	X	Cl	single bond	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	H
1134	X	Cl	single bond	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	CH <sub>3</sub>	H

SUBSTITUTE SHEET

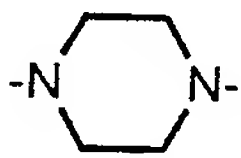
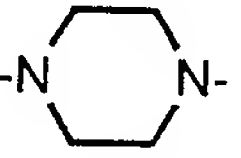
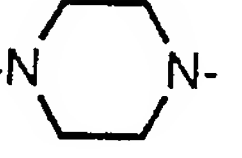
217

Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1135	X	Cl	single bond	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	C <sub>2</sub> H <sub>5</sub>	H
1136	X	Cl	single bond		*	H	COCH <sub>3</sub>
1137	X	Cl	single bond		H	H	COCH <sub>2</sub> Cl
1138	X	Cl	single bond		H	H	COC <sub>4</sub> H <sub>9</sub>
1139	X	Cl	single bond		H	CH <sub>3</sub>	COCH <sub>3</sub>
1140	X	Cl	single bond		H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
1141	X	Cl	single bond		*	H	H

SUBSTITUTE SHEET

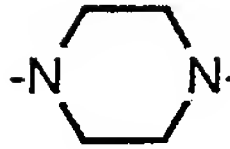
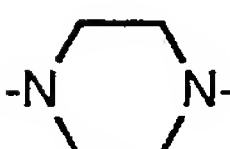
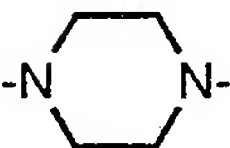


Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1142	X	Cl	single bond		H	CH <sub>3</sub>	H
1143	X	Cl	single bond		H	C <sub>2</sub> H <sub>5</sub>	H
1144	X	Cl	CH <sub>2</sub>	-NH-	H	H	COCH <sub>2</sub> Cl
1145	X	Cl	CH <sub>2</sub>	-NH-	H	H	COC <sub>4</sub> H <sub>9</sub>
1146	X	Cl	CH <sub>2</sub>	-NH-	H	CH <sub>3</sub>	COCH <sub>3</sub>
1147	X	Cl	CH <sub>2</sub>	-NH-	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
1148	X	Cl	CH <sub>2</sub>	-NH-	H	H	H
1149	X	Cl	CH <sub>2</sub>	-NH-	H	CH <sub>3</sub>	H
1150	X	Cl	CH <sub>2</sub>	-NH-	H	C <sub>2</sub> H <sub>5</sub>	H
1151	X	Cl	CH <sub>2</sub>	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>3</sub>
1152	X	Cl	CH <sub>2</sub>	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>2</sub> Cl

SUBSTITUTE SHEET

Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1153	X	Cl	CH <sub>2</sub>	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COC <sub>4</sub> H <sub>9</sub>
1154	X	Cl	CH <sub>2</sub>	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	CH <sub>3</sub>	COCH <sub>3</sub>
1155	X	Cl	CH <sub>2</sub>	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
1156	X	Cl	CH <sub>2</sub>	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	H
1157	X	Cl	CH <sub>2</sub>	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	CH <sub>3</sub>	H
1158	X	Cl	CH <sub>2</sub>	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	C <sub>2</sub> H <sub>5</sub>	H
1159	X	Cl	CH <sub>2</sub>		*	H	COCH <sub>3</sub>
1160	X	Cl	CH <sub>2</sub>		H	H	COCH <sub>2</sub> Cl
1161	X	Cl	CH <sub>2</sub>		H	H	COC <sub>4</sub> H <sub>9</sub>

SUBSTITUTE SHEET

220

Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1162	X	Cl	CH <sub>2</sub>		H	CH <sub>3</sub>	COCH <sub>3</sub>
1163	X	Cl	CH <sub>2</sub>		H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
1164	X	Cl	CH <sub>2</sub>		*	H	H
1165	X	Cl	CH <sub>2</sub>		H	CH <sub>3</sub>	H
1166	X	Cl	CH <sub>2</sub>		H	C <sub>2</sub> H <sub>5</sub>	H
1167	X	Cl	CH <sub>2</sub> CH <sub>2</sub>	-NH-	H	H	COCH <sub>3</sub>
1168	X	Cl	CH <sub>2</sub> CH <sub>2</sub>	-NH-	H	H	COCH <sub>2</sub> Cl
1169	X	Cl	CH <sub>2</sub> CH <sub>2</sub>	-NH-	H	H	COC <sub>4</sub> H <sub>9</sub>
1170	X	Cl	CH <sub>2</sub> CH <sub>2</sub>	-NH-	H	CH <sub>3</sub>	COCH <sub>3</sub>

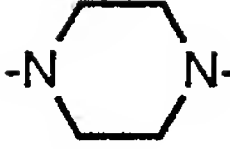
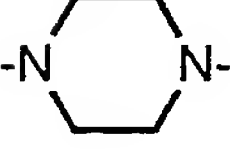
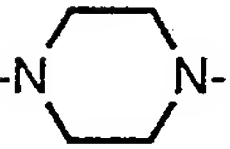
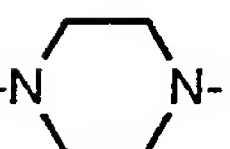
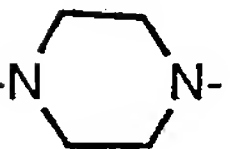

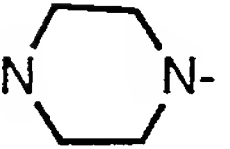

SUBSTITUTE SHEET



221

Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1171	X	Cl	CH <sub>2</sub> CH <sub>2</sub>	-NH-	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
1172	X	Cl	CH <sub>2</sub> CH <sub>2</sub>	-NH-	H	H	H
1173	X	Cl	CH <sub>2</sub> CH <sub>2</sub>	-NH-	H	CH <sub>3</sub>	H
1174	X	Cl	CH <sub>2</sub> CH <sub>2</sub>	-NH-	H	C <sub>2</sub> H <sub>5</sub>	H
1175	X	Cl	CH <sub>2</sub> CH <sub>2</sub>	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>3</sub>
1176	X	Cl	CH <sub>2</sub> CH <sub>2</sub>	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>2</sub> Cl
1177	X	Cl	CH <sub>2</sub> CH <sub>2</sub>	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COC <sub>4</sub> H <sub>9</sub>
1178	X	Cl	CH <sub>2</sub> CH <sub>2</sub>	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	CH <sub>3</sub>	COCH <sub>3</sub>
1179	X	Cl	CH <sub>2</sub> CH <sub>2</sub>	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
1180	X	Cl	CH <sub>2</sub> CH <sub>2</sub>	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	H
1181	X	Cl	CH <sub>2</sub> CH <sub>2</sub>	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	CH <sub>3</sub>	H
1182	X	Cl	CH <sub>2</sub> CH <sub>2</sub>	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	C <sub>2</sub> H <sub>5</sub>	H

SUBSTITUTE SHEET

Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1183	X	Cl	CH <sub>2</sub> CH <sub>2</sub>		*	H	COCH <sub>3</sub>
1184	X	Cl	CH <sub>2</sub> CH <sub>2</sub>		H	H	COCH <sub>2</sub> Cl
1185	X	Cl	CH <sub>2</sub> CH <sub>2</sub>		H	H	COC <sub>4</sub> H <sub>9</sub>
1186	X	Cl	CH <sub>2</sub> CH <sub>2</sub>		H	CH <sub>3</sub>	COCH <sub>3</sub>
1187	X	Cl	CH <sub>2</sub> CH <sub>2</sub>		H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
1188	X	Cl	CH <sub>2</sub> CH <sub>2</sub>		*	H	H
1189	X	Cl	CH <sub>2</sub> CH <sub>2</sub>		H	CH <sub>3</sub>	H
1190	X	Cl	CH <sub>2</sub> CH <sub>2</sub>		H	C <sub>2</sub> H <sub>5</sub>	H



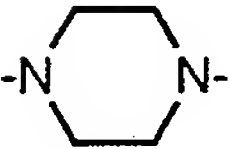


SUBSTITUTE SHEET

223

Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1191	X	Cl	C <sub>3</sub> H <sub>6</sub> (n)	-NH-	H	H	COCH <sub>3</sub>
1192	X	Cl	C <sub>3</sub> H <sub>6</sub> (n)	-NH-	H	H	COCH <sub>2</sub> Cl
1193	X	Cl	C <sub>3</sub> H <sub>6</sub> (n)	-NH-	H	H	COC <sub>4</sub> H <sub>9</sub>
1194	X	Cl	C <sub>3</sub> H <sub>6</sub> (n)	-NH-	H	CH <sub>3</sub>	COCH <sub>3</sub>
1195	X	Cl	C <sub>3</sub> H <sub>6</sub> (n)	-NH-	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
1196	X	Cl	C <sub>3</sub> H <sub>6</sub> (n)	-NH-	H	H	H
1197	X	Cl	C <sub>3</sub> H <sub>6</sub> (n)	-NH-	H	CH <sub>3</sub>	H
1198	X	Cl	C <sub>3</sub> H <sub>6</sub> (n)	-NH-	H	C <sub>2</sub> H <sub>5</sub>	H
1199	X	Cl	C <sub>3</sub> H <sub>6</sub> (n)	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>3</sub>
1200	X	Cl	C <sub>3</sub> H <sub>6</sub> (n)	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>2</sub> Cl
1201	X	Cl	C <sub>3</sub> H <sub>6</sub> (n)	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COC <sub>4</sub> H <sub>9</sub>
1202	X	Cl	C <sub>3</sub> H <sub>6</sub> (n)	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	CH <sub>3</sub>	COCH <sub>3</sub>

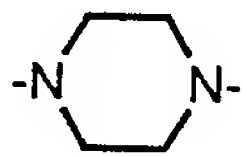
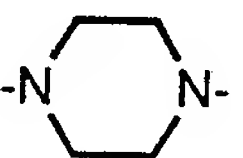
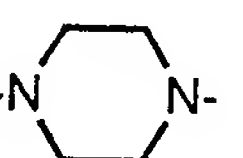
SUBSTITUTE SHEET

224

Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1203	X	Cl	C <sub>3</sub> H <sub>6</sub> (n)	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
1204	X	Cl	C <sub>3</sub> H <sub>6</sub> (n)	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	H
1205	X	Cl	C <sub>3</sub> H <sub>6</sub> (n)	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	CH <sub>3</sub>	H
1206	X	Cl	C <sub>3</sub> H <sub>6</sub> (n)	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	C <sub>2</sub> H <sub>5</sub>	H
1207	X	Cl	C <sub>3</sub> H <sub>6</sub> (n)		*	H	COCH <sub>3</sub>
1208	X	Cl	C <sub>3</sub> H <sub>6</sub> (n)		H	H	COCH <sub>2</sub> Cl
1209	X	Cl	C <sub>3</sub> H <sub>6</sub> (n)		H	H	COC <sub>4</sub> H <sub>9</sub>
1210	X	Cl	C <sub>3</sub> H <sub>6</sub> (n)		H	CH <sub>3</sub>	COCH <sub>3</sub>
1211	X	Cl	C <sub>3</sub> H <sub>6</sub> (n)		H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>

SUBSTITUTE SHEET

225

Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1212	X	Cl	C <sub>3</sub> H <sub>6</sub> (n)		*	H	H
1213	X	Cl	C <sub>3</sub> H <sub>6</sub> (n)		H	CH <sub>3</sub>	H
1214	X	Cl	C <sub>3</sub> H <sub>6</sub> (n)		H	C <sub>2</sub> H <sub>5</sub>	H
1215	X	Cl	C <sub>4</sub> H <sub>8</sub> (n)	-NH-	H	H	COCH <sub>3</sub>
1216	X	Cl	C <sub>4</sub> H <sub>8</sub> (n)	-NH-	H	H	COCH <sub>2</sub> Cl
1217	X	Cl	C <sub>4</sub> H <sub>8</sub> (n)	-NH-	H	H	COC <sub>4</sub> H <sub>9</sub>
1218	X	Cl	C <sub>4</sub> H <sub>8</sub> (n)	-NH-	H	CH <sub>3</sub>	COCH <sub>3</sub>
1219	CX	Cl	C <sub>4</sub> H <sub>8</sub> (n)	-NH-	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
1220	X	Cl	C <sub>4</sub> H <sub>8</sub> (n)	-NH-	H	H	H
1221	X	Cl	C <sub>4</sub> H <sub>8</sub> (n)	-NH-	H	CH <sub>3</sub>	H

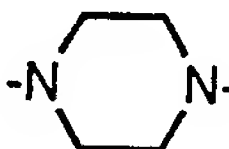

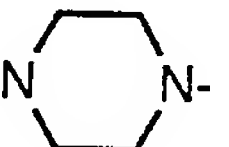
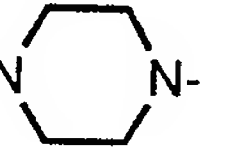
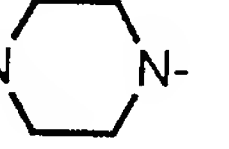
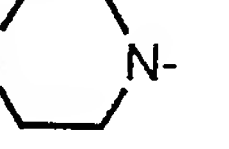


SUBSTITUTE SHEET

226

Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1222	X	Cl	C <sub>4</sub> H <sub>8</sub> (n)	-NH-	H	C <sub>2</sub> H <sub>5</sub>	H
1223	X	Cl	C <sub>4</sub> H <sub>8</sub> (n)	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>3</sub>
1224	X	Cl	C <sub>4</sub> H <sub>8</sub> (n)	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>2</sub> Cl
1225	X	Cl	C <sub>4</sub> H <sub>8</sub> (n)	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COC <sub>4</sub> H <sub>9</sub>
1226	X	Cl	C <sub>4</sub> H <sub>8</sub> (n)	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	CH <sub>3</sub>	COCH <sub>3</sub>
1227	X	Cl	C <sub>4</sub> H <sub>8</sub> (n)	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
1228	X	Cl	C <sub>4</sub> H <sub>8</sub> (n)	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	H
1229	X	Cl	C <sub>4</sub> H <sub>8</sub> (n)	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	CH <sub>3</sub>	H
1230	X	Cl	C <sub>4</sub> H <sub>8</sub> (n)	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	C <sub>2</sub> H <sub>5</sub>	H
1231	X	Cl	C <sub>4</sub> H <sub>8</sub> (n)		*	H	COCH <sub>3</sub>
1232	X	Cl	C <sub>4</sub> H <sub>8</sub> (n)		H	H	COCH <sub>2</sub> Cl




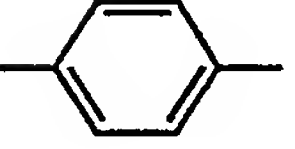
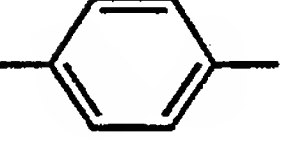
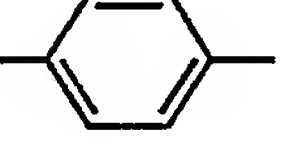
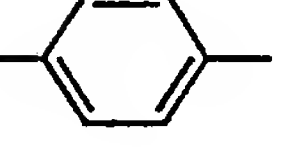
SUBSTITUTE SHEET

227

Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1233	X	Cl	C <sub>4</sub> H <sub>8</sub> (n)		H	H	COC <sub>4</sub> H <sub>9</sub>
1234	X	Cl	C <sub>4</sub> H <sub>8</sub> (n)		H	CH <sub>3</sub>	COCH <sub>3</sub>
1235	X	Cl	C <sub>4</sub> H <sub>8</sub> (n)		H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
1236	X	Cl	C <sub>4</sub> H <sub>8</sub> (n)		*	H	H
1237	X	Cl	C <sub>4</sub> H <sub>8</sub> (n)		H	CH <sub>3</sub>	H
1238	X	Cl	C <sub>4</sub> H <sub>8</sub> (n)		H	C <sub>2</sub> H <sub>5</sub>	H
1239	X	Cl		-NH-	H	H	COCH <sub>3</sub>
1240	X	Cl		-NH-	H	H	COCH <sub>2</sub> Cl

SUBSTITUTE SHEET






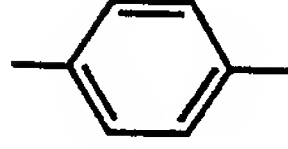
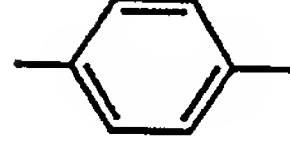


228

Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1241	X	Cl		-NH-	H	H	COC <sub>4</sub> H <sub>9</sub>
1242	X	Cl		-NH-	H	CH <sub>3</sub>	COCH <sub>3</sub>
1243	X	Cl		-NH-	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
1244	X	Cl		-NH-	H	H	H
1245	X	Cl		-NH-	H	CH <sub>3</sub>	H
1246	X	Cl		-NH-	H	C <sub>2</sub> H <sub>5</sub>	H
1247	X	Cl		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>3</sub>


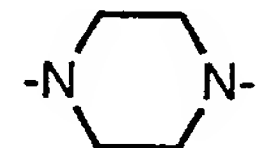

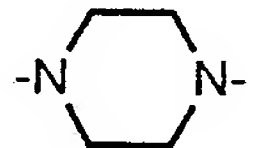
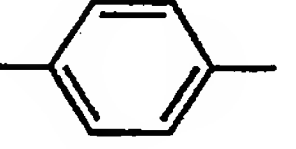
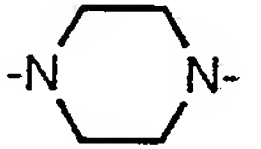
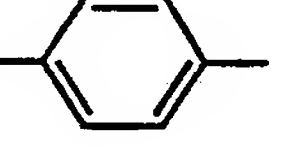
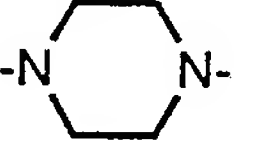
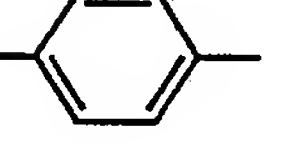
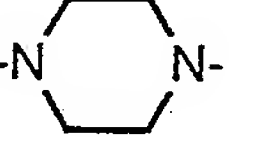
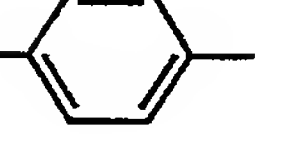
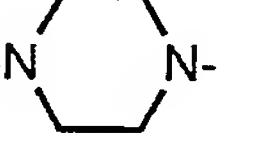
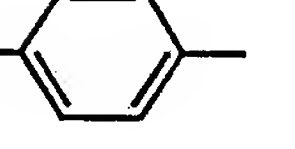
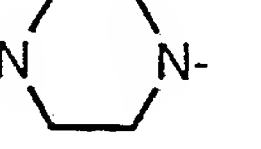
SUBSTITUTE SHEET



229

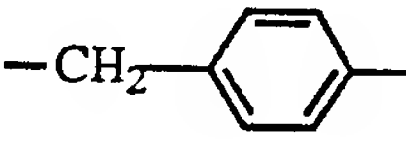
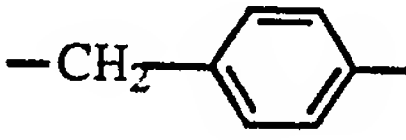
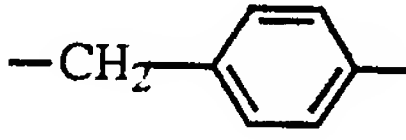
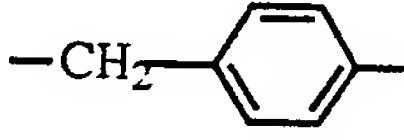
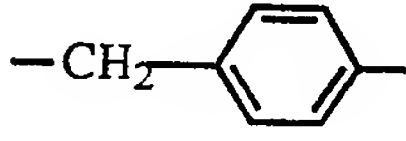
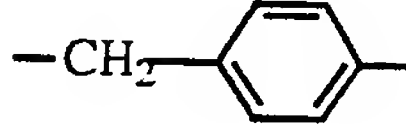
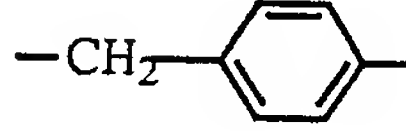
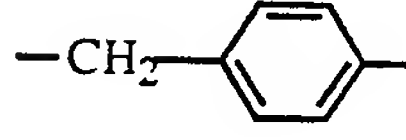
Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1248	X	Cl		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>2</sub> Cl
1249	X	Cl		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COC <sub>4</sub> H <sub>9</sub>
1250	X	Cl		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	CH <sub>3</sub>	COCH <sub>3</sub>
1251	X	Cl		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
1252	X	Cl		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	H
1253	X	Cl		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	CH <sub>3</sub>	H
1254	X	Cl		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	C <sub>2</sub> H <sub>5</sub>	H
1255	X	Cl			*	H	COCH <sub>3</sub>

SUBSTITUTE SHEET

Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1256	X	Cl			H	H	COCH <sub>2</sub> Cl
1257	X	Cl			H	H	COC <sub>4</sub> H <sub>9</sub>
1258	X	Cl			H	CH <sub>3</sub>	COCH <sub>3</sub>
1259	X	Cl			H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
1260	X	Cl			*	H	H
1261	X	Cl			H	CH <sub>3</sub>	H
1262	X	Cl			H	C <sub>2</sub> H <sub>5</sub>	H

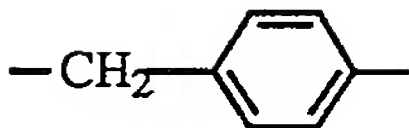
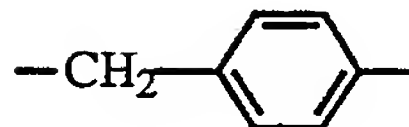
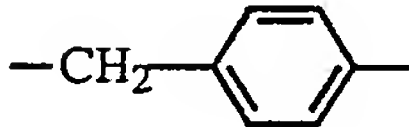
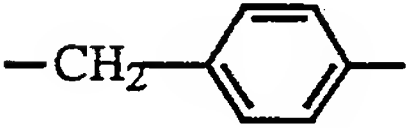
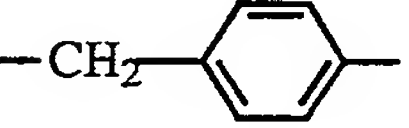
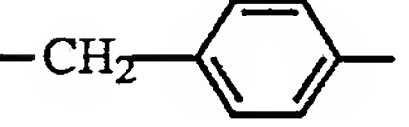
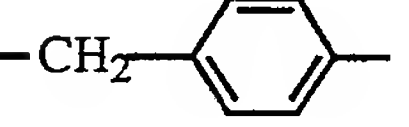
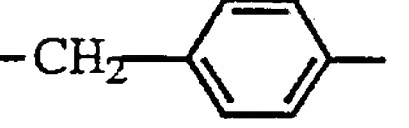
SUBSTITUTE SHEET

231

Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1263	X	Cl		-NH-	H	H	COCH <sub>3</sub>
1264	X	Cl		-NH-	H	H	COCH <sub>2</sub> Cl
1265	X	Cl		-NH-	H	H	COC <sub>4</sub> H <sub>9</sub>
1266	X	Cl		-NH-	H	CH <sub>3</sub>	COCH <sub>3</sub>
1267	X	Cl		-NH-	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
1268	X	Cl		-NH-	H	H	H
1269	X	Cl		-NH-	H	CH <sub>3</sub>	H
1270	X	Cl		-NH-	H	C <sub>2</sub> H <sub>5</sub>	H

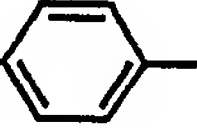

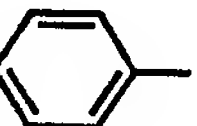
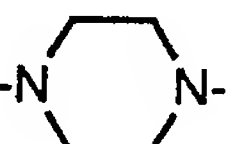
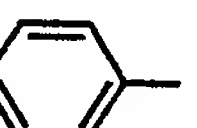

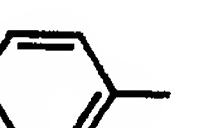

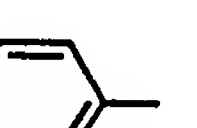
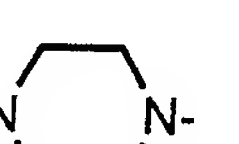
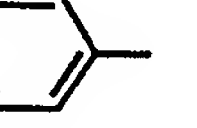
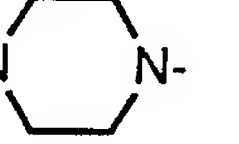
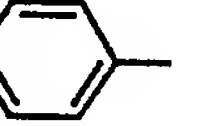

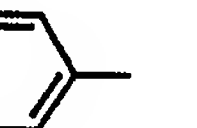
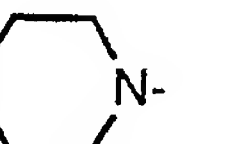
SUBSTITUTE SHEET

232

Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1271	X	Cl		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>3</sub>
1272	X	Cl		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>2</sub> Cl
1273	X	Cl		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COC <sub>4</sub> H <sub>9</sub>
1274	X	Cl		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	CH <sub>3</sub>	COCH <sub>3</sub>
1275	X	Cl		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
1276	X	Cl		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	H
1277	X	Cl		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	CH <sub>3</sub>	H
1278	X	Cl		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	C <sub>2</sub> H <sub>5</sub>	H


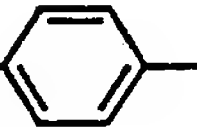
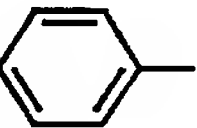
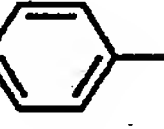
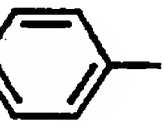
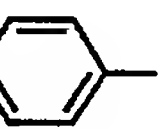
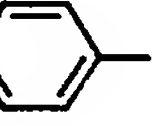
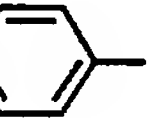
SUBSTITUTE SHEET

233

Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1279	X	Cl			*	H	COCH <sub>3</sub>
1280	X	Cl			H	H	COCH <sub>2</sub> Cl
1281	X	Cl			H	H	COC <sub>4</sub> H <sub>9</sub>
1282	X	Cl			H	CH <sub>3</sub>	COCH <sub>3</sub>
1283	X	Cl			H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
1284	X	Cl			*	H	H
1285	X	Cl			H	CH <sub>3</sub>	H
1286	X	Cl			H	C <sub>2</sub> H <sub>5</sub>	H



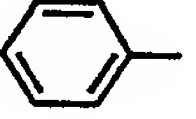
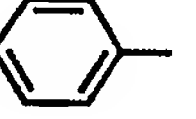
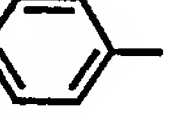
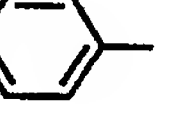
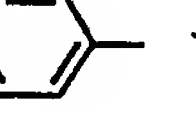
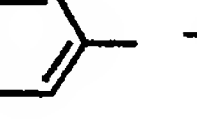
SUBSTITUTE SHEET

234

Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1287	X	Cl	$-\text{CH}_2\text{CH}_2-$ 	$-\text{NH}-$	H	H	$\text{COCH}_3$
1288	X	Cl	$-\text{CH}_2\text{CH}_2-$ 	$-\text{NH}-$	H	H	$\text{COCH}_2\text{Cl}$
1289	X	Cl	$-\text{CH}_2\text{CH}_2-$ 	$-\text{NH}-$	H	H	$\text{COC}_4\text{H}_9$
1290	X	Cl	$-\text{CH}_2\text{CH}_2-$ 	$-\text{NH}-$	H	$\text{CH}_3$	$\text{COCH}_3$
1291	X	Cl	$-\text{CH}_2\text{CH}_2-$ 	$-\text{NH}-$	H	$\text{C}_2\text{H}_5$	$\text{COCH}_3$
1292	X	Cl	$-\text{CH}_2\text{CH}_2-$ 	$-\text{NH}-$	H	H	H
1293	X	Cl	$-\text{CH}_2\text{CH}_2-$ 	$-\text{NH}-$	H	$\text{CH}_3$	H
1294	X	Cl	$-\text{CH}_2\text{CH}_2-$ 	$-\text{NH}-$	H	$\text{C}_2\text{H}_5$	H

SUBSTITUTE SHEET

235

Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1295 X	Cl			-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>3</sub>
1296 X	Cl			-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>2</sub> Cl
1297 X	Cl			-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COC <sub>4</sub> H <sub>9</sub>
1298 X	Cl			-NHCH <sub>2</sub> CH <sub>2</sub> -	H	CH <sub>3</sub>	COCH <sub>3</sub>
1299 X	Cl			-NHCH <sub>2</sub> CH <sub>2</sub> -	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
1300 X	Cl			-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	H
1301 X	Cl			-NHCH <sub>2</sub> CH <sub>2</sub> -	H	CH <sub>3</sub>	H
1302 X	Cl			-NHCH <sub>2</sub> CH <sub>2</sub> -	H	C <sub>2</sub> H <sub>5</sub>	H

SUBSTITUTE SHEET

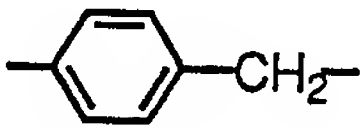
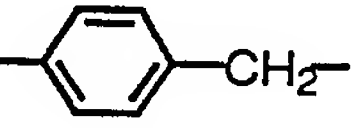
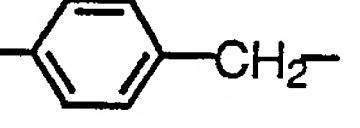
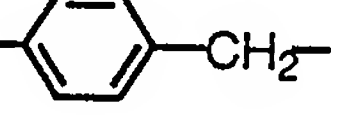
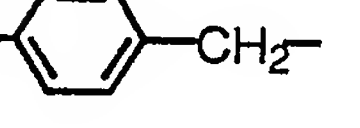
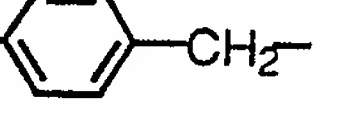
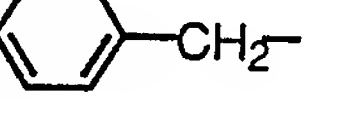
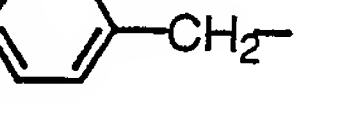
236

Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1303	X	Cl			*	H	COCH <sub>3</sub>
1304	X	Cl			H	H	COCH <sub>2</sub> Cl
1305	X	Cl			H	H	COC <sub>4</sub> H <sub>9</sub>
1306	X	Cl			H	CH <sub>3</sub>	COCH <sub>3</sub>
1307	X	Cl			H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
1308	X	Cl			*	H	H
1309	X	Cl			H	CH <sub>3</sub>	H
1310	X	Cl			H	C <sub>2</sub> H <sub>5</sub>	H

SUBSTITUTE SHEET

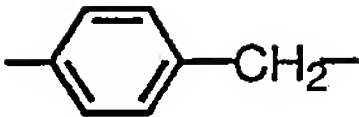
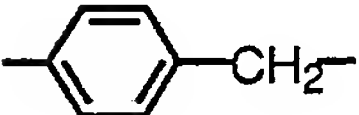
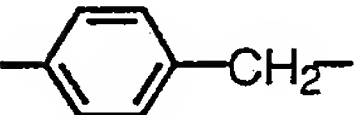
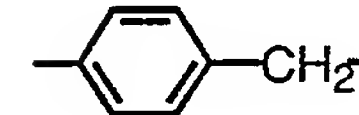
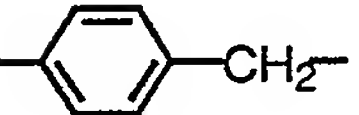
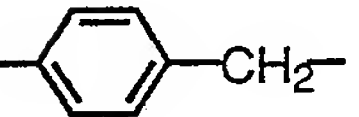
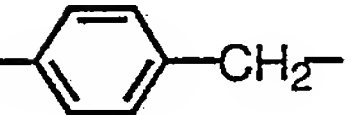
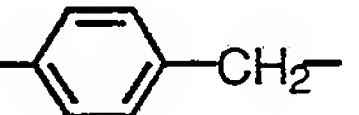


237

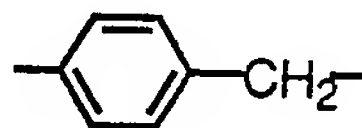
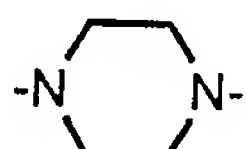
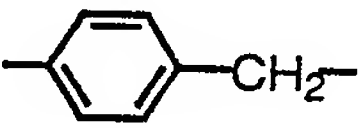
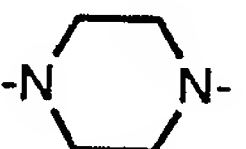
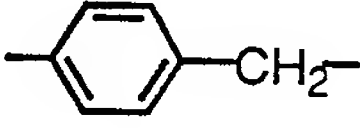

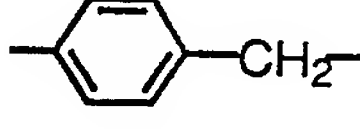
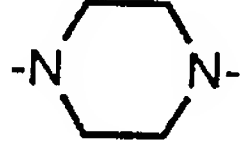
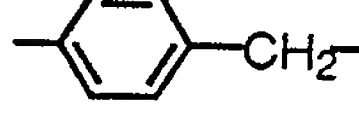
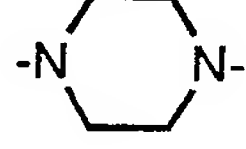
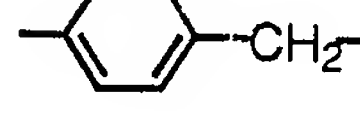
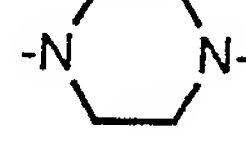
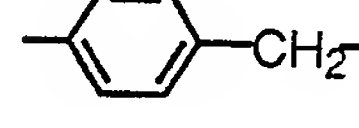
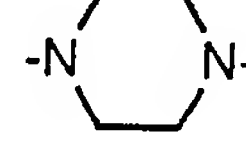

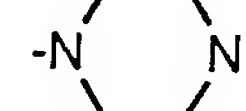
Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1311	X	Cl		-NH-	H	H	COCH <sub>3</sub>
1312	X	Cl		-NH-	H	H	COCH <sub>2</sub> Cl
1313	X	Cl		-NH-	H	H	COC <sub>4</sub> H <sub>9</sub>
1314	X	Cl		-NH-	H	CH <sub>3</sub>	COCH <sub>3</sub>
1315	X	Cl		-NH-	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
1316	X	Cl		-NH-	H	H	H
1317	X	Cl		-NH-	H	CH <sub>3</sub>	H
1318	X	Cl		-NH-	H	C <sub>2</sub> H <sub>5</sub>	H

SUBSTITUTE SHEET

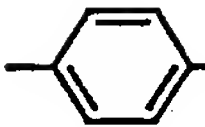
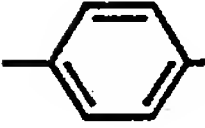
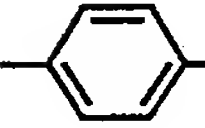





238

Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1319	X	Cl		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>3</sub>
1320	X	Cl		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>2</sub> Cl
1321	X	Cl		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COC <sub>4</sub> H <sub>9</sub>
1322	X	Cl		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	CH <sub>3</sub>	COCH <sub>3</sub>
1323	X	Cl		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
1324	X	Cl		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	H
1325	X	Cl		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	CH <sub>3</sub>	H
1326	X	Cl		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	C <sub>2</sub> H <sub>5</sub>	H

SUBSTITUTE SHEET








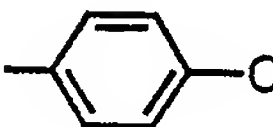
Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1327 X	Cl			*	H	COCH <sub>3</sub>	
1328 X	Cl			H	H	COCH <sub>2</sub> Cl	
1329 X	Cl			H	H	COC <sub>4</sub> H <sub>9</sub>	
1330 X	Cl			H	CH <sub>3</sub>	COCH <sub>3</sub>	
1331 X	Cl			H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>	
1332 X	Cl			*	H	H	
1333 X	Cl			H	CH <sub>3</sub>	H	
1334 X	Cl			H	C <sub>2</sub> H <sub>5</sub>	H	

SUBSTITUTE SHEET

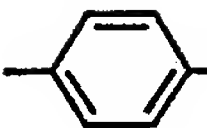
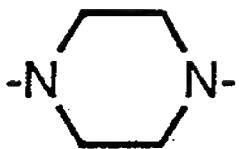
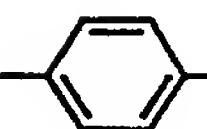
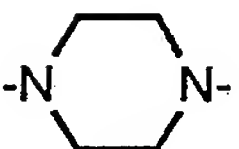

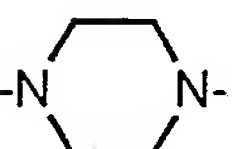

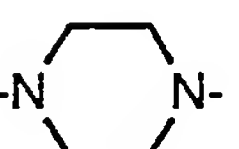

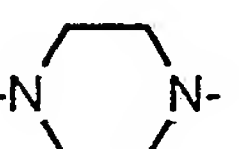

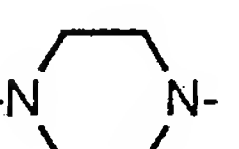

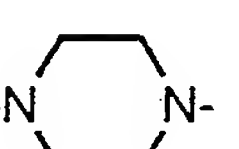

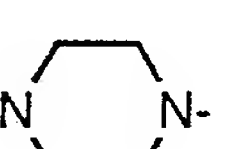
Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1335	X	Cl	 -CH <sub>2</sub> -CH <sub>2</sub> -	-NH-	H	H	COCH <sub>3</sub>
1336	X	Cl	 -CH <sub>2</sub> -CH <sub>2</sub> -	-NH-	H	H	COCH <sub>2</sub> Cl
1337	X	Cl	 -CH <sub>2</sub> -CH <sub>2</sub> -	-NH-	H	H	COC <sub>4</sub> H <sub>9</sub>
1338	X	Cl	 -CH <sub>2</sub> -CH <sub>2</sub> -	-NH-	H	CH <sub>3</sub>	COCH <sub>3</sub>
1339	X	Cl	 -CH <sub>2</sub> -CH <sub>2</sub> -	-NH-	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
1340	X	Cl	 -CH <sub>2</sub> -CH <sub>2</sub> -	-NH-	H	H	H
1341	X	Cl	 -CH <sub>2</sub> -CH <sub>2</sub> -	-NH-	H	CH <sub>3</sub>	H
1342	X	Cl	 -CH <sub>2</sub> -CH <sub>2</sub> -	-NH-	H	C <sub>2</sub> H <sub>5</sub>	H

SUBSTITUTE SHEET

241

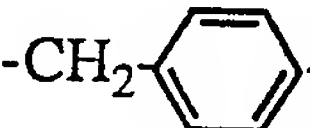
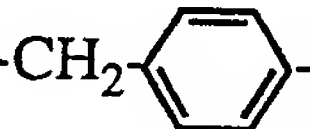
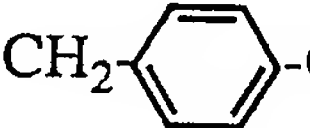
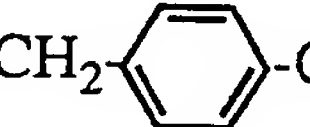
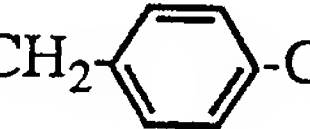
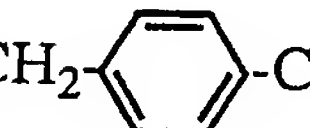


Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1343	X	Cl		-CH <sub>2</sub> -CH <sub>2</sub> -NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>3</sub>
1344	X	Cl		-CH <sub>2</sub> -CH <sub>2</sub> -NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>2</sub> Cl
1345	X	Cl		-CH <sub>2</sub> -CH <sub>2</sub> -NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COC <sub>4</sub> H <sub>9</sub>
1346	X	Cl		-CH <sub>2</sub> -CH <sub>2</sub> -NHCH <sub>2</sub> CH <sub>2</sub> -	H	CH <sub>3</sub>	COCH <sub>3</sub>
1347	X	Cl		-CH <sub>2</sub> -CH <sub>2</sub> -NHCH <sub>2</sub> CH <sub>2</sub> -	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
1348	X	Cl		-CH <sub>2</sub> -CH <sub>2</sub> -NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	H
1349	X	Cl		-CH <sub>2</sub> -CH <sub>2</sub> -NHCH <sub>2</sub> CH <sub>2</sub> -	H	CH <sub>3</sub>	H
1350	X	Cl		-CH <sub>2</sub> -CH <sub>2</sub> -NHCH <sub>2</sub> CH <sub>2</sub> -	H	C <sub>2</sub> H <sub>5</sub>	H

SUBSTITUTE SHEET

Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1351	X	Cl	 -CH <sub>2</sub> -CH <sub>2</sub> -	-N  -	*	H	COCH <sub>3</sub>
1352	X	Cl	 -CH <sub>2</sub> -CH <sub>2</sub> -	-N  -	H	H	COCH <sub>2</sub> Cl
1353	X	Cl	 -CH <sub>2</sub> -CH <sub>2</sub> -	-N  -	H	H	COC <sub>4</sub> H <sub>9</sub>
1354	X	Cl	 -CH <sub>2</sub> -CH <sub>2</sub> -	-N  -	H	CH <sub>3</sub>	COCH <sub>3</sub>
1355	X	Cl	 -CH <sub>2</sub> -CH <sub>2</sub> -	-N  -	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
1356	X	Cl	 -CH <sub>2</sub> -CH <sub>2</sub> -	-N  -	*	H	H
1357	X	Cl	 -CH <sub>2</sub> -CH <sub>2</sub> -	-N  -	H	CH <sub>3</sub>	H
1358	X	Cl	 -CH <sub>2</sub> -CH <sub>2</sub> -	-N  -	H	C <sub>2</sub> H <sub>5</sub>	H

SUBSTITUTE SHEET

243

Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1359 X	Cl			-NH-	H	H	COCH <sub>3</sub>
1360 X	Cl			NH-	H	H	COCH <sub>2</sub> Cl
1361 X	Cl			-NH-	H	H	COC <sub>4</sub> H <sub>9</sub>
1362 X	Cl			-NH-	H	CH <sub>3</sub>	COCH <sub>3</sub>
1363 X	Cl			-NH-	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
1364 X	Cl			-NH-	H	H	H
1365 X	Cl			-NH-	H	CH <sub>3</sub>	H
1366 X	Cl			-NH-	H	C <sub>2</sub> H <sub>5</sub>	H

SUBSTITUTE SHEET

Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1367	X	Cl	$-\text{CH}_2-\text{C}_6\text{H}_4-\text{CH}_2-$	$-\text{NHCH}_2\text{CH}_2-$	H	H	$\text{COCH}_3$
1368	X	Cl	$-\text{CH}_2-\text{C}_6\text{H}_4-\text{CH}_2-$	$-\text{NHCH}_2\text{CH}_2-$	H	H	$\text{COCH}_2\text{Cl}$
1369	X	Cl	$-\text{CH}_2-\text{C}_6\text{H}_4-\text{CH}_2-$	$-\text{NHCH}_2\text{CH}_2-$	H	H	$\text{COC}_4\text{H}_9$
1370	X	Cl	$-\text{CH}_2-\text{C}_6\text{H}_4-\text{CH}_2-$	$-\text{NHCH}_2\text{CH}_2-$	H	$\text{CH}_3$	$\text{COCH}_3$
1371	X	Cl	$-\text{CH}_2-\text{C}_6\text{H}_4-\text{CH}_2-$	$-\text{NHCH}_2\text{CH}_2-$	H	$\text{C}_2\text{H}_5$	$\text{COCH}_3$
1372	X	Cl	$-\text{CH}_2-\text{C}_6\text{H}_4-\text{CH}_2-$	$-\text{NHCH}_2\text{CH}_2-$	H	H	H
1373	X	Cl	$-\text{CH}_2-\text{C}_6\text{H}_4-\text{CH}_2-$	$-\text{NHCH}_2\text{CH}_2-$	H	$\text{CH}_3$	H
1374	X	Cl	$-\text{CH}_2-\text{C}_6\text{H}_4-\text{CH}_2-$	$-\text{NHCH}_2\text{CH}_2-$	H	$\text{C}_2\text{H}_5$	H

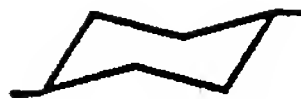

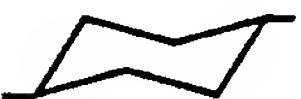
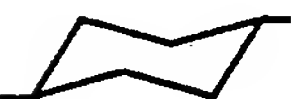

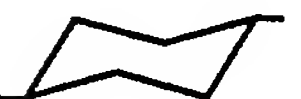
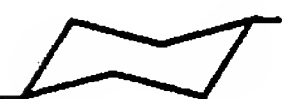


SUBSTITUTE SHEET



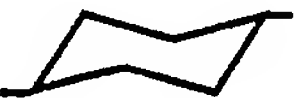
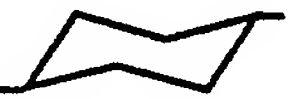

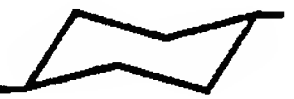


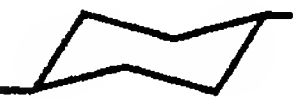
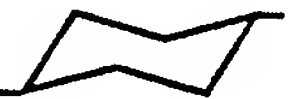
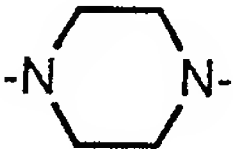
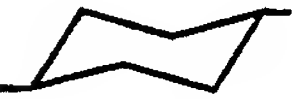

245

Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1375	X	Cl			*	H	COCH <sub>3</sub>
1376	X	Cl			H	H	COCH <sub>2</sub> Cl
1377	X	Cl			H	H	COC <sub>4</sub> H <sub>9</sub>
1378	X	Cl			H	CH <sub>3</sub>	COCH <sub>3</sub>
1379	X	Cl			H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
1380	X	Cl			*	H	H
1381	X	Cl			H	CH <sub>3</sub>	H
1382	X	Cl			H	C <sub>2</sub> H <sub>5</sub>	H

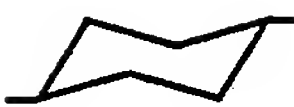
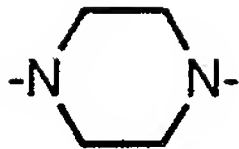


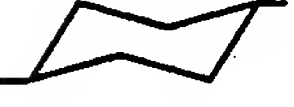
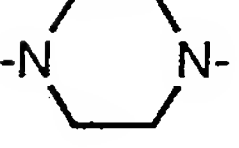
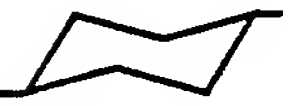
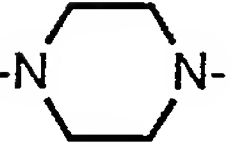

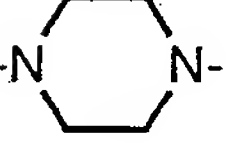

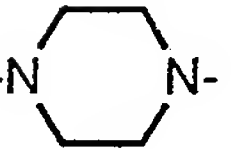

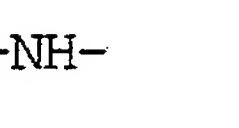

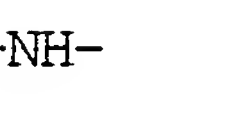
SUBSTITUTE SHEET

Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1383	X	Cl		-NH-	H	H	COCH <sub>3</sub>
1384	X	Cl		-NH-	H	H	COCH <sub>2</sub> Cl
1385	X	Cl		-NH-	H	H	COC <sub>4</sub> H <sub>9</sub>
1386	X	Cl		-NH-	H	CH <sub>3</sub>	COCH <sub>3</sub>
1387	X	Cl		-NH-	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
1388	X	Cl		-NH-	H	H	H
1389	X	Cl		-NH-	H	CH <sub>3</sub>	H
1390	X	Cl		-NH-	H	C <sub>2</sub> H <sub>5</sub>	H
1391	X	Cl		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>3</sub>


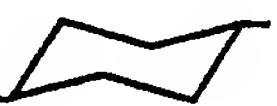






SUBSTITUTE SHEET

Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1392	X	Cl		-NHCH <sub>2</sub> CH <sub>2</sub> - H	H		COCH <sub>2</sub> Cl
1393	X	Cl		-NHCH <sub>2</sub> CH <sub>2</sub> - H	H		COC <sub>4</sub> H <sub>9</sub>
1394	X	Cl		-NHCH <sub>2</sub> CH <sub>2</sub> - H	CH <sub>3</sub>		COCH <sub>3</sub>
1395	X	Cl		-NHCH <sub>2</sub> CH <sub>2</sub> - H	C <sub>2</sub> H <sub>5</sub>		COCH <sub>3</sub>
1396	X	Cl		-NHCH <sub>2</sub> CH <sub>2</sub> - H	H		H
1397	X	Cl		-NHCH <sub>2</sub> CH <sub>2</sub> - H	CH <sub>3</sub>		H
1398	X	Cl		-NHCH <sub>2</sub> CH <sub>2</sub> - H	C <sub>2</sub> H <sub>5</sub>		H
1399	X	Cl		 *	H		COCH <sub>3</sub>
1400	X	Cl		 H	H		COCH <sub>2</sub> Cl

SUBSTITUTE SHEET






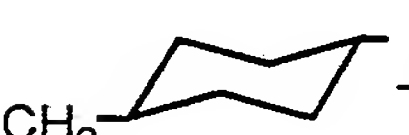



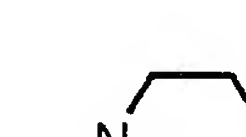
Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1401	X	Cl			H	H	COC <sub>4</sub> H <sub>9</sub>
1402	X	Cl			H	CH <sub>3</sub>	COCH <sub>3</sub>
1403	X	Cl			H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
1404	X	Cl			*	H	H
1405	X	Cl			H	CH <sub>3</sub>	H
1406	X	Cl			H	C <sub>2</sub> H <sub>5</sub>	H
1407	X	Cl			H	H	COCH <sub>3</sub>
1408	X	Cl			H	H	COCH <sub>2</sub> Cl

SUBSTITUTE SHEET

Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1409	X	Cl	-CH <sub>2</sub> - 	-NH-	H	H	COC <sub>4</sub> H <sub>9</sub>
1410	X	Cl	-CH <sub>2</sub> - 	-NH-	H	CH <sub>3</sub>	COCH <sub>3</sub>
1411	X	Cl	-CH <sub>2</sub> - 	-NH-	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
1412	X	Cl	-CH <sub>2</sub> - 	-NH-	H	H	H
1413	X	Cl	-CH <sub>2</sub> - 	-NH-	H	CH <sub>3</sub>	H
1414	X	Cl	-CH <sub>2</sub> - 	-NH-	H	C <sub>2</sub> H <sub>5</sub>	H
1415	X	Cl	-CH <sub>2</sub> - 	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>3</sub>
1416	X	Cl	-CH <sub>2</sub> - 	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>2</sub> Cl






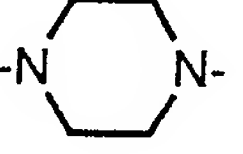
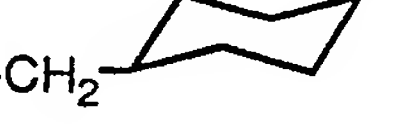
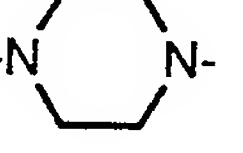

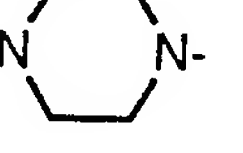

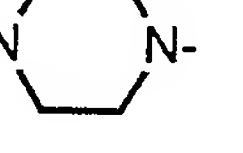
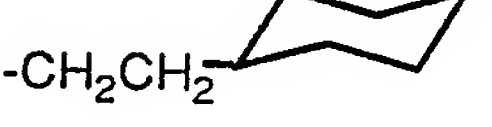
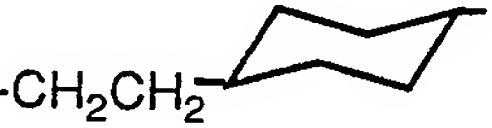
SUBSTITUTE SHEET

250


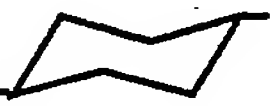


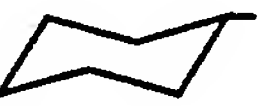


Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1417	X	Cl		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COC <sub>4</sub> H <sub>9</sub>
1418	X	Cl		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	CH <sub>3</sub>	COCH <sub>3</sub>
1419	X	Cl		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
1420	X	Cl		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	H
1421	X	Cl		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	CH <sub>3</sub>	H
1422	X	Cl		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	C <sub>2</sub> H <sub>5</sub>	H
1423	X	Cl			*	H	COCH <sub>3</sub>
1424	X	Cl			H	H	COCH <sub>2</sub> Cl

SUBSTITUTE SHEET

251








Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1425	X	Cl			H	H	COC <sub>4</sub> H <sub>9</sub>
1426	X	Cl			H	CH <sub>3</sub>	COCH <sub>3</sub>
1427	X	Cl			H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
1428	X	Cl			*	H	H
1429	X	Cl			H	CH <sub>3</sub>	H
1430	X	Cl			H	C <sub>2</sub> H <sub>5</sub>	H
1431	X	Cl		-NH-	H	H	COCH <sub>3</sub>
1432	X	Cl		-NH-	H	H	COCH <sub>2</sub> Cl

SUBSTITUTE SHEET

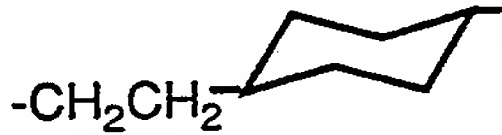
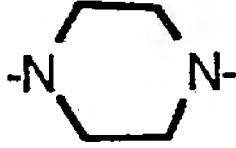
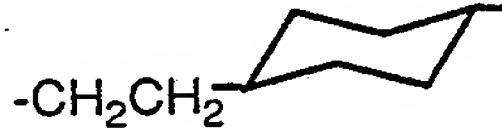
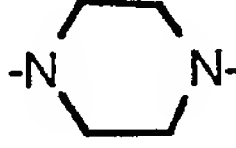
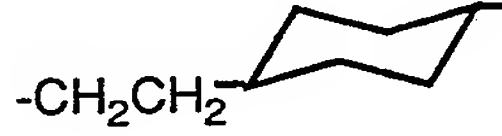
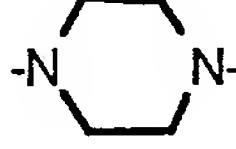
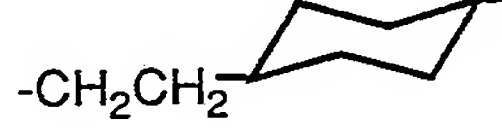

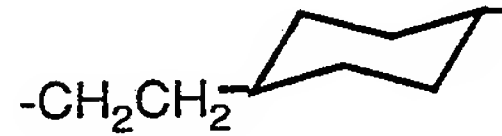
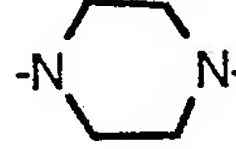
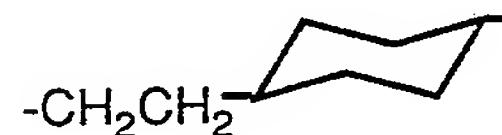
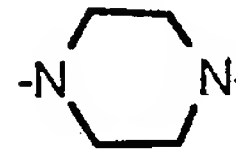
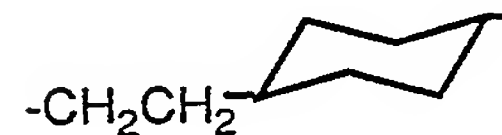
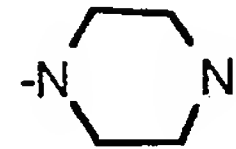
Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1433	X	Cl	-CH <sub>2</sub> CH <sub>2</sub> - 	-NH-	H	H	COC <sub>4</sub> H <sub>9</sub>
1434	X	Cl	-CH <sub>2</sub> CH <sub>2</sub> - 	-NH-	H	CH <sub>3</sub>	COCH <sub>3</sub>
1435	X	Cl	-CH <sub>2</sub> CH <sub>2</sub> - 	-NH-	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
1436	X	Cl	-CH <sub>2</sub> CH <sub>2</sub> - 	-NH-	H	H	H
1437	X	Cl	-CH <sub>2</sub> CH <sub>2</sub> - 	-NH-	H	CH <sub>3</sub>	H
1438	X	Cl	-CH <sub>2</sub> CH <sub>2</sub> - 	-NH-	H	C <sub>2</sub> H <sub>5</sub>	H
1439	X	Cl	-CH <sub>2</sub> CH <sub>2</sub> - 	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>3</sub>

SUBSTITUTE SHEET

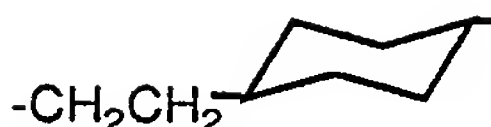









Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1440	X	Cl	-CH <sub>2</sub> CH <sub>2</sub> - 	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>2</sub> Cl
1441	X	Cl	-CH <sub>2</sub> CH <sub>2</sub> - 	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COC <sub>4</sub> H <sub>9</sub>
1442	X	Cl	-CH <sub>2</sub> CH <sub>2</sub> - 	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	CH <sub>3</sub>	COCH <sub>3</sub>
1443	X	Cl	-CH <sub>2</sub> CH <sub>2</sub> - 	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
1444	X	Cl	-CH <sub>2</sub> CH <sub>2</sub> - 	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	H
1445	X	Cl	-CH <sub>2</sub> CH <sub>2</sub> - 	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	CH <sub>3</sub>	H
1446	X	Cl	-CH <sub>2</sub> CH <sub>2</sub> - 	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	C <sub>2</sub> H <sub>5</sub>	H

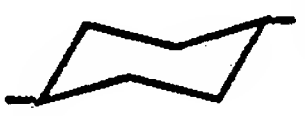
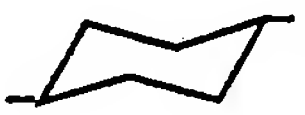
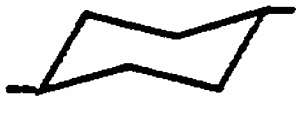

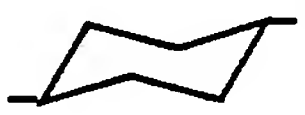
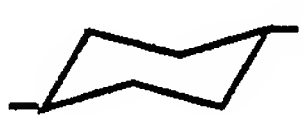


SUBSTITUTE SHEET

Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1447	X	Cl			*	H	COCH <sub>3</sub>
1448	X	Cl			H	H	COCH <sub>2</sub> Cl
1449	X	Cl			H	H	COC <sub>4</sub> H <sub>9</sub>
1450	X	Cl			H	CH <sub>3</sub>	COCH <sub>3</sub>
1451	X	Cl			H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
1452	X	Cl			*	H	H
1453	X	Cl			H	CH <sub>3</sub>	H








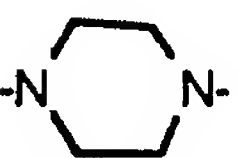

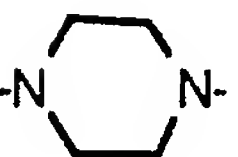

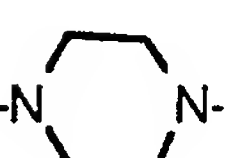
SUBSTITUTE SHEET

Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1454	X	Cl			H	C <sub>2</sub> H <sub>5</sub>	H
1455	X	Cl		-NH-	H	H	COCH <sub>3</sub>
1456	X	Cl		-NH-	H	H	COCH <sub>2</sub> Cl
1457	X	Cl		-NH-	H	H	COC <sub>4</sub> H <sub>9</sub>
1458	X	Cl		-NH-	H	CH <sub>3</sub>	COCH <sub>3</sub>
1459	X	Cl		-NH-	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
1460	X	Cl		-NH-	H	H	H


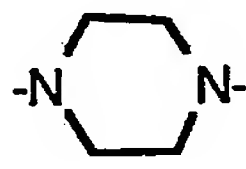



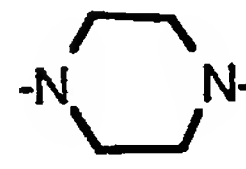



SUBSTITUTE SHEET

Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1461	X	Cl	 CH <sub>2</sub> -	-NH-	H	CH <sub>3</sub>	H
1462	X	Cl	 CH <sub>2</sub> -	-NH-	H	C <sub>2</sub> H <sub>5</sub>	H
1463	X	Cl	 CH <sub>2</sub> -	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>3</sub>
1464	X	Cl	 CH <sub>2</sub> -	-NH-	H	H	COCH <sub>2</sub> Cl
1465	X	Cl	 CH <sub>2</sub> -	-NH-	H	H	COC <sub>4</sub> H <sub>9</sub>
1466	X	Cl	 CH <sub>2</sub> -	-NH-	H	CH <sub>3</sub>	COCH <sub>3</sub>
1467	X	Cl	 CH <sub>2</sub> -	-NH-	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
1468	X	Cl	 CH <sub>2</sub> -	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	H

257

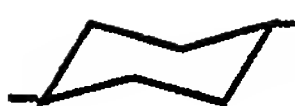








Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1469	X	Cl		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	CH <sub>3</sub>	H
1470	X	Cl		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	C <sub>2</sub> H <sub>5</sub>	H
1471	X	Cl			*	H	COCH <sub>3</sub>
1472	X	Cl			H	H	COCH <sub>2</sub> Cl
1473	X	Cl			H	H	COC <sub>4</sub> H <sub>9</sub>
1474	X	Cl			H	CH <sub>3</sub>	COCH <sub>3</sub>
1475	X	Cl			H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>

SUBSTITUTE SHEET

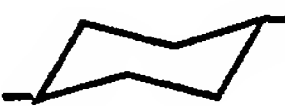
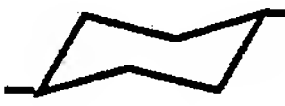
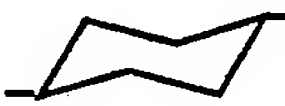
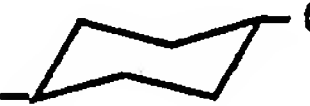


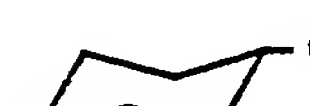
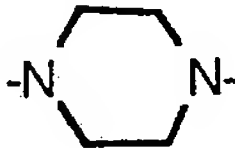

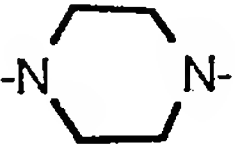

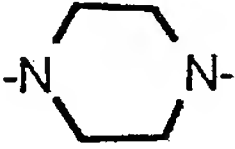


Ex.#	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1476	X	Cl			*	H	H
1477	X	Cl			H	CH <sub>3</sub>	H
1478	X	Cl			H	C <sub>2</sub> H <sub>5</sub>	H
1479	X	Cl		-NH-	H	H	COCH <sub>3</sub>
1480	X	Cl		-NH-	H	H	COCH <sub>2</sub> Cl
1481	X	Cl		-NH-	H	H	COC <sub>4</sub> H <sub>9</sub>

SUBSTITUTE SHEET

259

Ex. #	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1482	X	Cl	 CH <sub>2</sub> CH <sub>2</sub> -	-NH-	H	CH <sub>3</sub>	COCH <sub>3</sub>
1483	X	Cl	 CH <sub>2</sub> CH <sub>2</sub> -	-NH-	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
1484	X	Cl	 CH <sub>2</sub> CH <sub>2</sub> -	-NH-	H	H	H
1485	X	Cl	 CH <sub>2</sub> CH <sub>2</sub> -	-NH-	H	CH <sub>3</sub>	H
1486	X	Cl	 CH <sub>2</sub> CH <sub>2</sub> -	-NH-	H	C <sub>2</sub> H <sub>5</sub>	H
1487	X	Cl	 CH <sub>2</sub> CH <sub>2</sub> -	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>3</sub>
1488	X	Cl	 CH <sub>2</sub> CH <sub>2</sub> -	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>2</sub> Cl
1489	X	Cl	 CH <sub>2</sub> CH <sub>2</sub> -	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COC <sub>4</sub> H <sub>9</sub>
1490	X	Cl	 CH <sub>2</sub> CH <sub>2</sub> -	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	CH <sub>3</sub>	COCH <sub>3</sub>

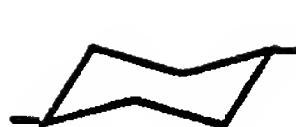
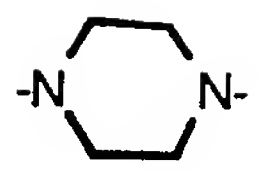
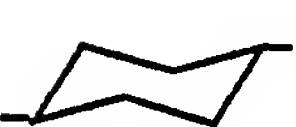
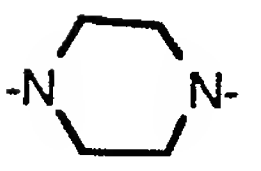
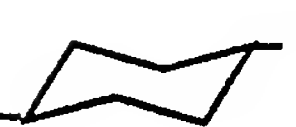
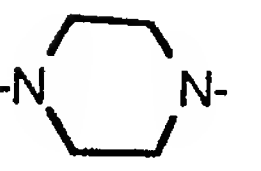
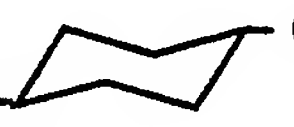




SUBSTITUTE SHEET

Ex. #	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1491	X	Cl	 CH <sub>2</sub> CH <sub>2</sub> -	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>
1492	X	Cl	 CH <sub>2</sub> CH <sub>2</sub> -	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	H
1493	X	Cl	 CH <sub>2</sub> CH <sub>2</sub> -	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	CH <sub>3</sub>	H
1494	X	Cl	 CH <sub>2</sub> CH <sub>2</sub> -	-NHCH <sub>2</sub> CH <sub>2</sub> -	H	C <sub>2</sub> H <sub>5</sub>	H
1495	X	Cl	 CH <sub>2</sub> CH <sub>2</sub> -		*	H	COCH <sub>3</sub>
1496	X	Cl	 CH <sub>2</sub> CH <sub>2</sub> -		H	H	COCH <sub>2</sub> Cl
1497	X	Cl	 CH <sub>2</sub> CH <sub>2</sub> -		H	H	COC <sub>4</sub> H <sub>9</sub>
1498	X	Cl	 CH <sub>2</sub> CH <sub>2</sub> -		H	CH <sub>3</sub>	COCH <sub>3</sub>
1499	X	Cl	 CH <sub>2</sub> CH <sub>2</sub> -		H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>

SUBSTITUTE SHEET



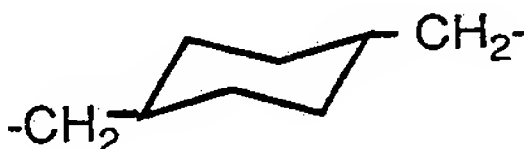
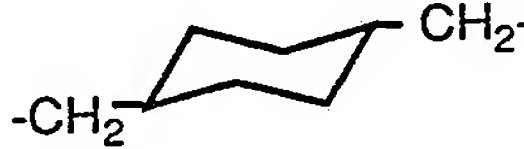
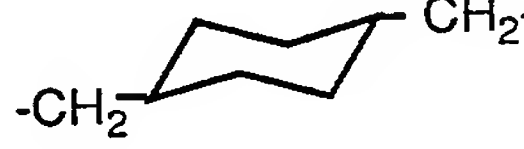

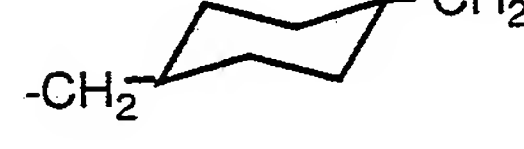
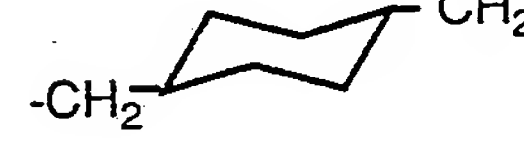


261

Ex. #	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1500	X	Cl	 CH <sub>2</sub> CH <sub>2</sub> -		*	H	H
1501	X	Cl	 CH <sub>2</sub> CH <sub>2</sub> -		H	CH <sub>3</sub>	H
1502	X	Cl	 CH <sub>2</sub> CH <sub>2</sub> -		H	C <sub>2</sub> H <sub>5</sub>	H
1503	X	Cl	-CH <sub>2</sub> -  -CH <sub>2</sub> -	-NH-	H	H	COCH <sub>3</sub>
1504	X	Cl	-CH <sub>2</sub> -  -CH <sub>2</sub> -	-NH-	H	H	COCH <sub>2</sub> Cl
1505	X	Cl	-CH <sub>2</sub> -  -CH <sub>2</sub> -	-NH-	H	H	COC <sub>4</sub> H <sub>9</sub>
1506	X	Cl	-CH <sub>2</sub> -  -CH <sub>2</sub> -	-NH-	H	CH <sub>3</sub>	COCH <sub>3</sub>
1507	X	Cl	-CH <sub>2</sub> -  -CH <sub>2</sub> -	-NH-	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>

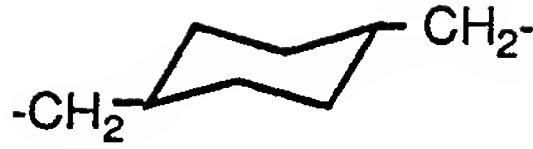
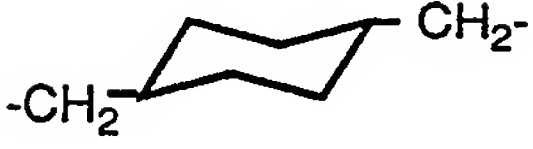

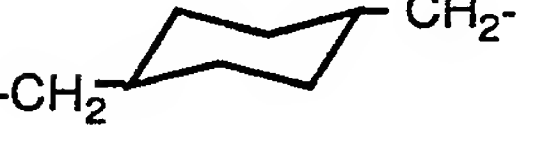


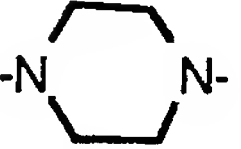

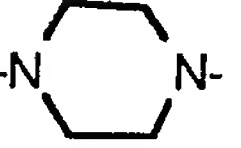

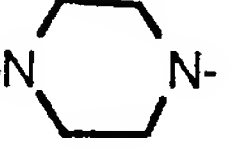

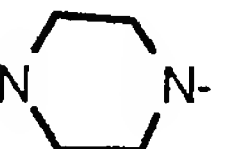
SUBSTITUTE SHEET

262

Ex. #	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1508	X	Cl		-NH-	H	H	H
1509	X	Cl		-NH-	H	CH <sub>3</sub>	H
1510	X	Cl		-NH-	H	C <sub>2</sub> H <sub>5</sub>	H
1511	X	Cl		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>3</sub>
1512	X	Cl		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COCH <sub>2</sub> Cl
1513	X	Cl		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	COC <sub>4</sub> H <sub>9</sub>
1514	X	Cl		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	CH <sub>3</sub>	COCH <sub>3</sub>
1515	X	Cl		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>

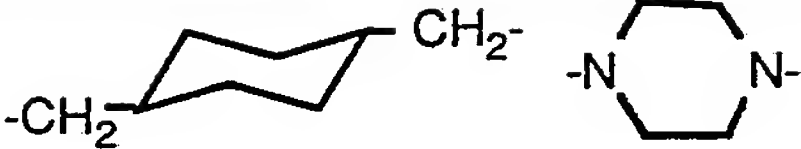
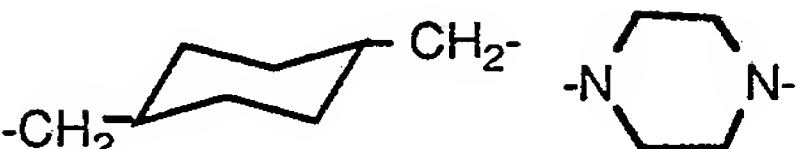
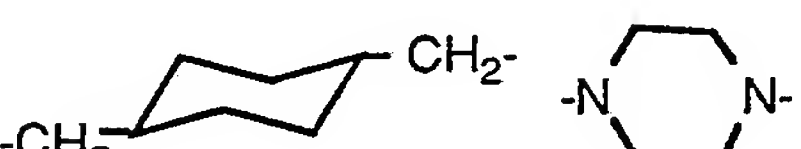
SUBSTITUTE SHEET

263

Ex. #	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1516	X	Cl		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	H	H
1517	X	Cl		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	CH <sub>3</sub>	H
1518	X	Cl		-NHCH <sub>2</sub> CH <sub>2</sub> -	H	C <sub>2</sub> H <sub>5</sub>	H
1519	X	Cl			*	H	COCH <sub>3</sub>
1520	X	Cl			H	H	COCH <sub>2</sub> Cl
1521	X	Cl			H	H	COC <sub>4</sub> H <sub>9</sub>
1522	X	Cl			H	CH <sub>3</sub>	COCH <sub>3</sub>
1523	X	Cl			H	C <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>

SUBSTITUTE SHEET

264

Ex. #	R <sup>1</sup>	R <sup>2</sup>	A	L	B	E	P
1524	X	Cl			*	H	H
1525	X	Cl			H	CH <sub>3</sub>	H
1526	X	Cl			H	C <sub>2</sub> H <sub>5</sub>	H

SUBSTITUTE SHEET

**BIOLOGICAL EVALUATION**

Compounds of Examples 1-80 are suitable  
angiotension II antagonists for use as the first component  
5 of conjugates of the invention. The AII receptor binding  
activity of many of the Example #1-#80 compounds, for  
example, is described in EP #253,310 published  
20 January 1988. The compound of Example #5 was further  
evaluated in three biological assays (Assays "A", "B" and  
10 "C") for AII antagonist and blood pressure lowering  
properties. In two other assays, blood-pressure lowering  
effects of the conjugate of Example #81 were evaluated  
(Assays "D" and "E").

15 Assay A: Angiotensin II Binding Activity

Compound of Example #5 was tested for ability to  
bind to the smooth muscle angiotensin II receptor using a  
rat uterine membrane preparation. Angiotensin II (AII) was  
20 purchased from Peninsula Labs.  $^{125}\text{I}$ -angiotensin II  
(specific activity of 2200 Ci/mmol) was purchased from Du  
Pont-New England Nuclear. Other chemicals were obtained  
from Sigma Chemical Co. This assay was carried out  
according to the method of Douglas et al [Endocrinology,  
25 106, 120-124 (1980)]. Rat uterine membranes were prepared  
from fresh tissue. All procedures were carried out at 4°C.  
Uteri were stripped of fat and homogenized in phosphate-  
buffered saline at pH 7.4 containing 5 mM EDTA. The  
homogenate was centrifuged at 1500 x g for 20 min., and the  
30 supernatant was recentrifuged at 100,000 x g for 60 min.  
The pellet was resuspended in buffer consisting of 2 mM  
EDTA and 50 mM Tris-HCl (pH 7.5) to a final protein  
concentration of 4 mg/ml. Assay tubes were charged with  
0.25 ml of a solution containing 5 mM  $\text{MgCl}_2$ , 2 mM EDTA,  
35 0.5% bovine serum albumin, 50 mM Tris-HCl, pH 7.5 and  $^{125}\text{I}$ -  
AII (approximately  $10^5$  cpm) in the absence or in the  
presence of unlabelled ligand. The reaction was initiated  
by the addition of membrane protein and the mixture was

incubated at 25°C for 60 min. The incubation was terminated with ice-cold 50 mM Tris-HCl (pH 7.5) and the mixture was filtered to separate membrane-bound labelled peptide from the free ligand. The incubation tube and filter were washed with ice-cold buffer. Filters were assayed for radioactivity in a Micromedic gamma counter. Nonspecific binding was defined as binding in the presence of 10  $\mu$ M of unlabelled AII. Specific binding was calculated as total binding minus nonspecific binding. The receptor binding affinity of an AII antagonist compound was indicated by the concentration (IC<sub>50</sub>) of the tested AII antagonist which gives 50% displacement of the total specifically bound <sup>125</sup>I-AII from the high affinity AII receptor. Binding data were analyzed by a nonlinear least-squares curve fitting program. Results are reported in Table VIII.

Assay B: In Vitro Vascular Smooth Muscle-Response for AII

Compound of Example #5 was tested for AII antagonist activity in rabbit aortic rings. Male New Zealand white rabbits (2-2.5 kg) were sacrificed using an overdose of pentobarbital and exsanguinated via the carotid arteries. The thoracic aorta was removed, cleaned of adherent fat and connective tissue and then cut into 3-mm ring segments. The endothelium was removed from the rings by gently sliding a rolled-up piece of filter paper into the vessel lumen. The rings were then mounted in a water-jacketed tissue bath, maintained at 37°C, between moveable and fixed ends of a stainless steel wire with the moveable end attached to an FT03 Grass transducer coupled to a Model 7D Grass Polygraph for recording isometric force responses. The bath was filled with 20 ml of oxygenated (95% oxygen/5% carbon dioxide) Krebs solution of the following composition (nM): 130 NaCl, 15 NaHCO<sub>3</sub>, 15 KCl, 1.2 NaH<sub>2</sub>PO<sub>4</sub>, 1.2 MgSO<sub>4</sub>, 2.5 CaCl<sub>2</sub>, and 11.4 glucose. The preparations were equilibrated for one hour before approximately one gram of passive tension was placed on the rings. Angiotensin II concentration-response curves were then recorded ( $3 \times 10^{-10}$

to  $1 \times 10^{-5}$  M). Each concentration of AII was allowed to elicit its maximal contraction, and then AII was washed out repeatedly for 30 minutes before rechallenging with a higher concentration of AII. Aorta rings were exposed to the test antagonist at  $10^{-5}$  M for 5 minutes before challenging with AII. Adjacent segments of the same aorta ring were used for all concentration-response curves in the presence or absence of the test antagonist. The effectiveness of the test compound was expressed in terms of  $pA_2$  values and were calculated according to H.O. Schild [Br. J. Pharmacol. Chemother., 2,189-206 (1947)]. The  $pA_2$  value is the concentration of the test antagonist compound which increases the  $EC_{50}$  value for AII by a factor of two. The test compound was evaluated in aorta rings from three rabbits. Results are reported in Table VIII.

TABLE VIII

In Vitro Angiotensin II  
Activity of Compounds of Formula I

Test Compound	<sup>1</sup> Assay A IC <sub>50</sub> (nM)	<sup>2</sup> Assay B PA <sub>2</sub>
Ex. #5	216 ± 45	7.13 ± 0.16

<sup>1</sup>Assay A: In Vitro angiotensin II Binding Activity

<sup>2</sup>Assay B: In Vitro Vascular Smooth Muscle Response

Assay C: In Vivo Intraduodenal and Intravenous Pressor  
Assay Response for AII Antagonists

The in vivo AII receptor antagonist activity of Example #5 compound was examined in ganglion-blocked male Sprague-Dawley rats (Harlan Sprague-Dawley, Inc.), weighing 300-400 g, anesthetized with 100 mg/kg i.p. Inactin. Catheters (PE-50) were implanted in a femoral artery and vein to measure mean arterial pressure and to administer compounds, respectively. A tracheal catheter maintained airway patency. For intravenous experiments, autonomic neurotransmission was blocked by treatment with mecamylamine (3 mg/kg i.v.) and atropine (400 µg/kg i.v.). AII (30 ng/kg i.v., 20-25 µl volume) was administered four times at 10 minute intervals to establish a reproducible control pressor response. Example #5 compound was then administered at 1, 3 and 10 mg/kg in separate groups of rats as an intravenous bolus (0.2 ml volume) before rechallenging with AII



(30 ng/kg, 20-25  $\mu$ l volume) for the following 2 hours. For intraduodenal experiments, rats were anesthetized as above, but ganglion blockade was not performed. AII was administered at 100 ng/kg i.v. (20-25  $\mu$ l volume), and  
5 was administered at 10, 30 and 100 mg/kg in separate groups of rats as an intraduodenal bolus (0.2 ml volume). Angiotensin II injections were then given 5, 10, 20, 30, 45, 60, 75, 90, and 120 minutes after  
10 administration of the test compound and response of arterial pressure was monitored. The response to AII was calculated as percent of the control response and then the percent inhibition was calculated as 100 minus the percent control response. Duration of action of a  
15 test compound was defined as the time from peak percent inhibition to 50% of peak. The test compound was tested in two rats and the values for the two rats were averaged. Results are reported in Tables IX and X as percent of the control of AII pressor response, where "control" is defined as AII pressor response before the  
20 AII antagonist test compound is administered.

270

TABLE IX

In Vivo Intravenous Angiotensin II

Activity of Example #5 Compound

(% Control of AII Pressor Response)

5

	<u>Dose</u> <u>(mg/kg)</u>	<u>Time (min)</u>										
		1	5	10	20	30	40	50	60	75	90	120
10	1	80	85	92	90	88	86	86	89	93	95	100
	n=4	±3	±4	±4	±6	±5	±5	±6	±5	±3	±5	±0
15	3	39	55	63	68	74	75	75	81	88	92	98
	n=4	±5	±7	±8	±6	±7	±5	±3	±7	±7	±5	±1
	10	4	16	23	31	40	47	51	60	71	80	96
	n=6	±2	±2	±2	±2	±3	±4	±4	±6	±7	±8	±6

20

**SUBSTITUTE SHEET**

271

TABLE X

In Vivo Intraduodenal Angiotensin II Activity  
of Example #5 Compound  
(% Control of AII Pressor Response)

	Dose mg/kg	<u>Time (min)</u>								
		1	5	10	20	30	40	50	60	75
10	10 n=3	100 ±0	94 ±4	99 ±1	85 ±11	91 ±9	91 ±9	95 ±5	93 ±7	95 ±5
	30 n=4	48 ±4	48 ±7	44 ±11	28 ±5	34 ±4	42 ±6	41 ±0	53 ±2	74 ±7
15	100 n=4	28 ±3	19 ±4	15 ±3	14 ±8	9 ±5	5 ±2	13 ±6	10 ±4	13 ±5

**SUBSTITUTE SHEET**

Assay D: In Vivo Effects of Chronic Infusion of  
Conjugate of the Invention

A conjugate of the invention as synthesized  
5 in Example 81 was evaluated biologically by an *in vivo*  
assay to determine the ability of the conjugate to  
selectively inhibit renal action and thereby control  
blood pressure. This *in vivo* experiment was conducted  
to characterize the effects of the Example 81 conjugate  
10 on spontaneously hypertensive rats (SHR) by acute  
administration i.v. and by chronic administration i.v.  
The Example 81 compound or saline vehicle was infused  
continuously for four days in SHR. Mean arterial  
pressure was measured (Gould Chart Recorder, model 3800;  
15 Statham P23Db pressure transducer) via an indwelling  
femoral artery catheter between 10:00 A. M. and 2:00 P.  
M. each day. The Example 81 conjugate (10 mg/hr) or  
saline was infused via a jugular vein catheter with a  
Harvard infusion pump. After administration of the  
20 Example 81 conjugate, there was observed a lowered mean  
arterial pressure as compared to the saline vehicle  
control as reported in Table XI and also in Fig. 1. A  
test was conducted to determine whether the Example 81  
conjugate would antagonize non-renal, vascular  
25 angiotensin II receptors. In this test AII was  
administered by bolus injection (100 ng/kg) to the SHR  
rats (described above) on the control day and on days 1,  
2 and 3 during conjugate infusion. No evidence for  
systemic angiotensin II receptor antagonism was  
30 observed, given the similar pressor responses to  
injections of angiotensin II on the control day and days  
1, 2 and 3 of infusion of the Example 81 conjugate as  
shown in Table XII and also in Figure 2.

273

TABLE XI

Effect of Ex. #81 Conjugate on Mean  
Arterial Pressure: Chronic Administration

5

Time (days):	Control	1	2	3
MAP (mm Hg)	163	148	135	140

10

TABLE XII

15

Effect of Ex. #81 Conjugate on  
AIL Pressor Response

Time (days):	Control	1	2	3
MAP (mm Hg)	44	45	65	60

**SUBSTITUTE SHEET**

Assay "E": In Vivo Effects of Acute Infusion of Conjugate of the Invention

In this assay, a comparison was made between an  
5 angiotensin II antagonist compound (Ex. #5) and a glutamyl  
conjugate (Ex. #81) of the Ex. #5 AII antagonist compound  
to determine the renal selectivity of the conjugate. Male  
Sprague-Dawley rats (300-350 g body weight) had catheters  
10 implanted into the femoral artery and vein under chloral  
hydrate anesthesia (400 mg/kg, i.p.). After 2 to 4 days of  
recovery, on the experimental day, a urinary bladder  
catheter was implanted under methohexital anesthesia  
(50 mg/kg, i.p.). Rats were placed in a restraint device  
to allow for urine collection and mean arterial pressure  
15 measurements. After 1-2 hours of recovery, in conscious  
rats, an isotonic saline infusion (50  $\mu$ l/min) was started  
and continued for the duration of the experiment. After  
one hour equilibration to the saline infusion, a 20 minute  
control urine and mean arterial pressure collection were  
20 obtained. Then angiotensin II was infused at 20 ng/min for  
25 minutes. After 5 minutes of angiotensin II infusion, a  
20 minute experimental collection was made. Finally, 5  
minutes after the end of angiotensin II infusion, a 20  
minute recovery collection was obtained. In separate  
25 groups of rats, vehicle (0.3 ml isotonic saline, i.v.  
bolus), Example #5 angiotensin II antagonist compound  
(100 mg/kg, i.v. bolus), or Example #81 conjugate  
(100 mg/kg, i.v. bolus) was administered 1-2 minutes prior  
to onset of angiotensin II infusion. Infusion of  
30 angiotensin II increased mean arterial pressure and  
decreased urinary sodium excretion. The Example #5 AII  
antagonist compound prevented both responses to angiotensin  
II. The Example #81 conjugate had no effect on the mean  
arterial pressure response but prevented the  
35 antinatriuretic response to angiotensin II. Angiotensin II  
infusion following administration of Example #81 conjugate  
actually increased urinary sodium excretion, probably due  
to a pressure natriuresis. Results are shown in Tables

XIII and XIV and also in Figs. 3 and 4. Data are presented as means  $\pm$  SE. Repeated measures analysis of variance was used for main effects and interactions and Tukey's HSD test was used for pairwise comparisons among means. Statistical significance was defined as  $p < 0.05$ .

276

TABLE XIII

Effect of Ex. #81 Conjugate on  
Urinary Sodium Excretion ( $\mu$ Eq/min/100 g BW)

5		Control	AII	Recovery
	Vehicle	1.9 $\pm$ 0.8	0.8 $\pm$ 0.3*	1.7 $\pm$ 0.5
	Ex. #5	2.4 $\pm$ 0.5	2.5 $\pm$ 1.1	2.6 $\pm$ 0.7
10	Ex. #81	1.3 $\pm$ 0.3	4.1 $\pm$ 1.3*	1.8 $\pm$ 0.4

15

TABLE XIV

Effect of Ex. #81 Conjugate on Mean  
Arterial Pressure (mm Hg): Acute Administration

20

		Control	AII	Recovery
	Vehicle (n=6)	121 $\pm$ 3	155 $\pm$ 3*	123 $\pm$ 4
	Ex. #5 (n=6)	123 $\pm$ 5	125 $\pm$ 7	124 $\pm$ 7
25	Ex. #81 (n=6)	117 $\pm$ 3	151 $\pm$ 4*	121 $\pm$ 4

30

**SUBSTITUTE SHEET**



Also embraced within this invention is a class of pharmaceutical compositions comprising one or more conjugates which comprises a first component selected from angiotensin II antagonist compounds of Formula I linked to  
5 a second component provided by an enzyme-cleavable moiety. Such pharmaceutical compositions further comprise one or more non-toxic, pharmaceutically acceptable carriers and/or diluents and/or adjuvants (collectively referred to herein as "carrier" materials) and, if desired, other active  
10 ingredients. The conjugates of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. Therapeutically effective doses of a conjugate of the  
15 present invention required to prevent or arrest the progress of the medical condition are readily ascertained by one of ordinary skill in the art. The conjugates and composition may, for example, be administered intra-vascularly, intraperitoneally, subcutaneously, intra-  
20 muscularly or topically.

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical  
25 composition is preferably made in the form of a dosage unit containing a particular amount of the conjugate. Examples of such dosage units are tablets or capsules. These may with advantage contain an amount of conjugate from about 1 to 250 mg, preferably from about 25 to 150 mg. A suitable  
30 daily dose for a mammal may vary widely depending on the condition of the patient and other factors. However, a dose of from about 0.1 to 3000 mg/kg body weight, particularly from about 1 to 100 mg/kg body weight, may be appropriate.

The conjugate may also be administered by injection as a composition wherein, for example, saline, dextrose or water may be used as a suitable carrier. A suitable daily dose is from about 0.1 to 100 mg/kg body weight injected per day in multiple doses depending on the disease being treated. A preferred daily dose would be from about 1 to 30 mg/kg body weight. Conjugates indicated for prophylactic therapy will preferably be administered in a daily dose generally in a range from about 0.1 mg to about 100 mg per kilogram of body weight per day. A more preferred dosage will be a range from about 1 mg to about 100 mg per kilogram of body weight. Most preferred is a dosage in a range from about 1 to about 50 mg per kilogram of body weight per day. A suitable dose can be administered, in multiple sub-doses per day. These sub-doses may be administered in unit dosage forms. Typically, a dose or sub-dose may contain from about 1 mg to about 100 mg of active compound per unit dosage form. A more preferred dosage will contain from about 2 mg to about 50 mg of active compound per unit dosage form. Most preferred is a dosage form containing from about 3 mg to about 25 mg of active compound per unit dose.

The dosage regimen for treating a disease condition with the conjugates and/or compositions of this invention is selected in accordance with a variety of factors, including the type, age, weight, sex and medical condition of the patient, the severity of the disease, the route of administration, and the particular conjugate employed, and thus may vary widely.

For therapeutic purposes, the conjugates of this invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered per os, the conjugate may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanolic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium

and calcium salts of phosphoric and sulfuric acids,  
gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone,  
and/or polyvinyl alcohol, and then tableted or encapsulated  
for convenient administration. Such capsules or tablets  
5 may contain a controlled-release formulation as may be  
provided in a dispersion of conjugate in  
hydroxypropylmethyl cellulose. Formulations for parenteral  
administration may be in the form of aqueous or non-aqueous  
isotonic sterile injection solutions or suspensions. These  
10 solutions and suspensions may be prepared from sterile  
powders or granules having one or more of the carriers or  
diluent mentioned for use in the formulations for oral  
administration. The conjugates may be dissolved in water,  
polyethylene glycol, propylene glycol, ethanol, corn oil,  
15 cottonseed oil, peanut oil, sesame oil, benzyl alcohol,  
sodium chloride, and/or various buffers. Other adjuvants  
and modes of administration are well and widely known in  
the pharmaceutical art.

20                   Although this invention has been described with  
respect to specific embodiments, the details of these  
embodiments are not to be construed as limitations.  
Various equivalents, changes and modifications may be made  
without departing from the spirit and scope of this  
25 invention, and it is understood that such equivalent  
embodiments are part of this invention.

WHAT IS CLAIMED IS:

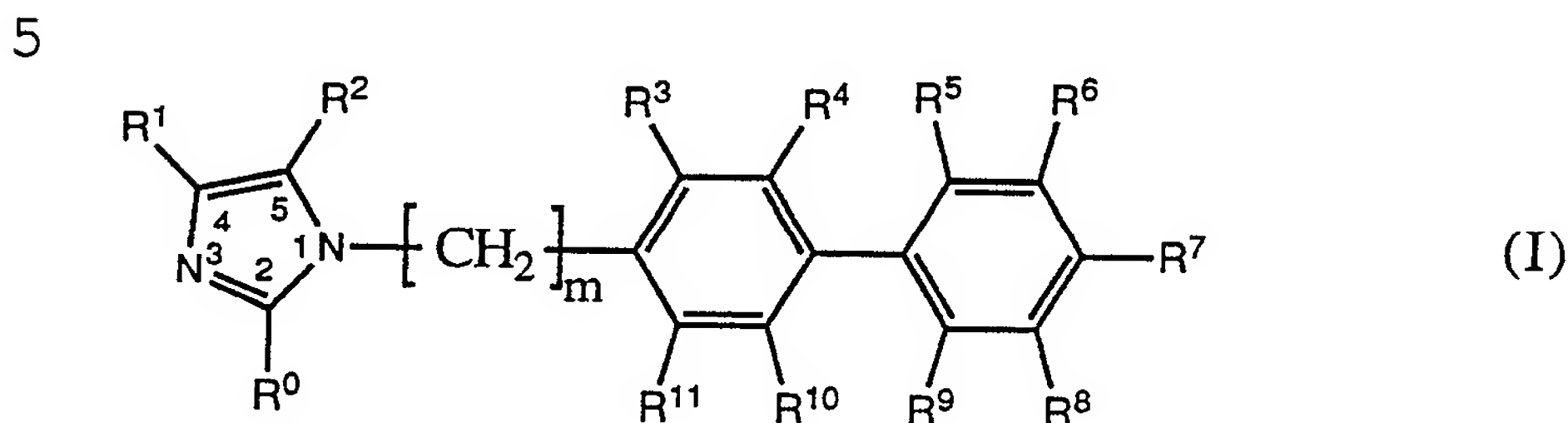
1. A conjugate comprising a residue of an  
angiotensin II antagonist compound, said conjugate being  
5 renal selective.

2. Conjugate of Claim 1 comprising a first  
residue and a second residue, said first and second  
residues connected together by a cleavable bond, wherein  
10 said first residue is provided by an angiotensin II  
antagonist compound, and wherein said second residue is  
capable of being cleaved from said first residue  
selectivity in the kidney.

3. Conjugate of Claim 2 wherein said first  
and second residues are provided by precursor compounds  
wherein the precursor compound of one of said first and  
second residues has a reactable carboxylic acid moiety  
and the precursor of the other of said first and second  
20 residues has a reactable amino moiety or a moiety  
convertible to a reactable amino moiety, whereby a  
cleavable bond may be formed between said carboxylic  
acid moiety and said amino moiety.

4. Conjugate of Claim 3 wherein said  
angiotensin II antagonist compound providing said first  
residue is selected from biphenylmethyl 1H-substituted-1,3-  
imidazole compounds.

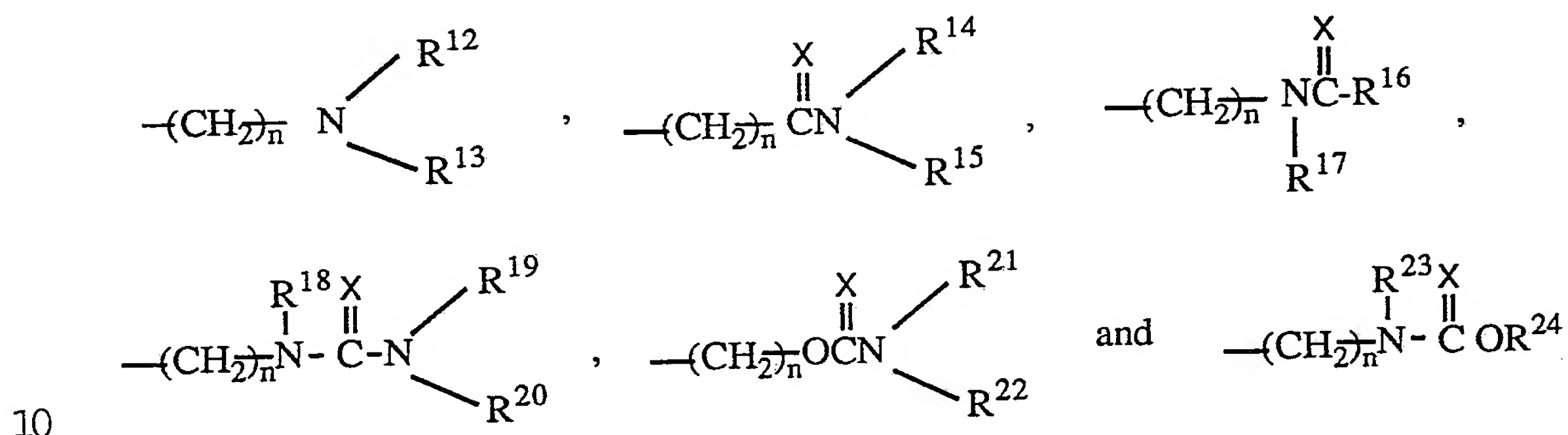
5. Conjugate of Claim 4 wherein said angiotensin II antagonist compound is selected from a class of compounds defined by Formula I:



wherein m is a number selected from one to four, inclusive;

10 wherein each of R<sup>0</sup> through R<sup>11</sup> is independently selected from hydrido, alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, formyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkylcarbonylalkyl, alkoxycarbonyl, alkenyl, 15 cycloalkenyl, alkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, mercaptocarbonyl, mercaptothiocarbonyl, mercaptoalkyl, alkoxycarbonyloxy, 20 alkylthio, cycloalkylthio, alkylthiocarbonyl, alkylcarbonylthio, alkylthiocarbonyloxy, alkylthiocarbonylthio, alkylthiothiocarbonyl, alkylthiothiocarbonylthio, arylthio, arylthiocarbonyl, arylcarbonylthio, arylthiocarbonyloxy, 25 arylthiocarbonylthio, arylthiothiocarbonyl, arylthiothiocarbonylthio, aralkylthio, aralkylthiocarbonyl, aralkylcarbonylthio, aralkylthiocarbonyloxy, aralkylthiocarbonylthio, alkylthiocarbonyl, aralkylthiocarbonylthio, mercapto, alkylsulfinyl, 30 alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl,

arylsulfinyl, arylsulfonyl, phthalimido, phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and cycloheteroalkylcarbonylalkyl wherein each of said heteroaryl- and cyclohetero-containing groups has one or more ring atoms selected from oxygen, sulfur and nitrogen atoms, and wherein each of  $R^0$  through  $R^{11}$  may be further independently selected from amino and amido radicals of the formula



wherein X is oxygen atom or sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

wherein each of  $R^{12}$  through  $R^{24}$  is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl, and wherein  $R^{12}$  and  $R^{13}$  taken together,  $R^{14}$  and  $R^{15}$  taken together,  $R^{16}$  and  $R^{17}$  taken together,  $R^{19}$  and  $R^{20}$  taken together and  $R^{21}$  and  $R^{22}$  taken together may each form a heterocyclic group having five to seven ring members including the nitrogen atom of said amino or amido radical and which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms and which heterocyclic group may be saturated or partially unsaturated; wherein  $R^{12}$  and  $R^{13}$  taken together,  $R^{14}$  and  $R^{15}$  taken together,  $R^{19}$  and  $R^{20}$  taken together and  $R^{21}$  and  $R^{22}$  taken together may each form an aromatic heterocyclic



group having five ring members including the nitrogen atom  
of said amino or amido radical and which aromatic  
heterocyclic group may further contain one or more hetero  
atoms as ring atoms selected from oxygen, nitrogen and  
5 sulfur atoms;

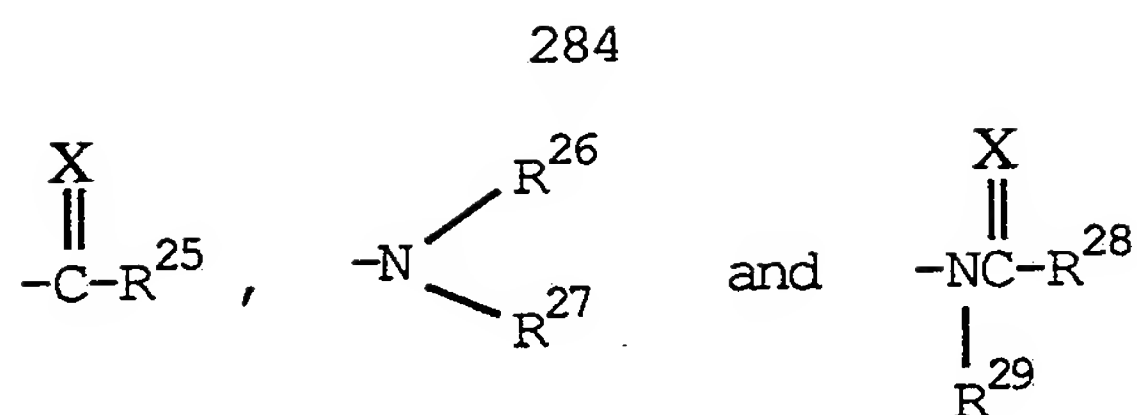
and wherein each of  $R^3$  through  $R^{11}$  may be further  
independently selected from hydrido and haloalkyl, and from  
acidic moieties of the formula

10

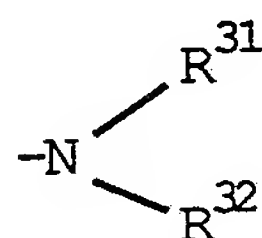


wherein n is a number selected from zero through three,  
inclusive, and wherein A is an acidic group selected to  
15 contain at least one acidic hydrogen atom, and the amide,  
ester and salt derivatives of said acidic moieties; wherein  
Y is a spacer group independently selected from one or more  
of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl,  
aryl, aralkyl and heteroaryl having one or more ring atoms  
20 selected from oxygen, sulfur and nitrogen atoms;

and wherein any of the foregoing  $R^1$  through  $R^{24}$ , Y and A  
groups having a substitutable position may be substituted  
with one or more groups selected from hydroxy, alkyl,  
25 alkenyl, alkynyl, aralkyl, hydroxyalkyl, trifluoromethyl,  
difluoroalkyl, oxo, alkoxy, aryloxy, aralkoxy, aralkylthio,  
alkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, aroyl,  
cycloalkenyl, cyano, cyanoamino, nitro, alkylcarbonyloxy,  
alkoxycarbonyloxy, alkylcarbonyl, alkoxycarbonyl, carboxyl,  
30 mercapto, mercaptocarbonyl, alkylthio, arylthio,  
alkylthiocarbonyl, alkylsulfinyl, alkylsulfonyl,  
aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl,  
arylsulfonyl, heteroaryl having one or more ring atoms  
selected from oxygen, sulfur and nitrogen atoms, and amino  
35 and amido radicals of the formula

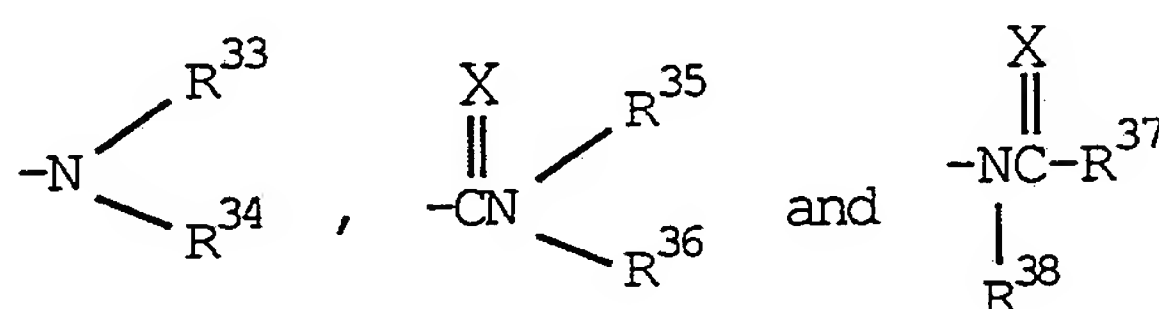


wherein X is selected from oxygen atom and sulfur atom;  
 wherein R<sup>25</sup> is selected from hydrido, alkyl, cycloalkyl,  
 5 cycloalkylalkyl, aralkyl, aryl, DR<sup>30</sup> and



wherein D is selected from oxygen atom and sulfur atom and  
 10 R<sup>30</sup> is selected from hydrido, alkyl, cycloalkyl,  
 cycloalkylalkyl, aralkyl and aryl; wherein each of R<sup>25</sup>,  
 R<sup>26</sup>, R<sup>27</sup>, R<sup>28</sup>, R<sup>29</sup>, R<sup>31</sup> and R<sup>32</sup> is independently selected  
 from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl,  
 haloalkyl, cycloalkylalkyl, alkoxyalkyl, alkylcarbonyl,  
 15 alkoxycarbonyl, carboxyl, alkylsulfinyl, alkylsulfonyl,  
 arylsulfinyl, arylsulfonyl, haloalkylsulfinyl,  
 haloalkylsulfonyl, aralkyl and aryl, and wherein each of  
 R<sup>26</sup>, R<sup>27</sup>, R<sup>28</sup>, R<sup>29</sup>, R<sup>31</sup> and R<sup>32</sup> is further independently  
 selected from amino and amido radicals of the formula

20



wherein X is oxygen atom or sulfur atom;

25 wherein each of R<sup>33</sup>, R<sup>34</sup>, R<sup>35</sup>, R<sup>36</sup>, R<sup>37</sup> and R<sup>38</sup> is  
 independently selected from hydrido, alkyl, cycloalkyl,  
 cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl,  
 cycloalkylalkyl, alkoxyalkyl, haloalkylsulfinyl,  
 haloalkylsulfonyl, aralkyl and aryl, and wherein R<sup>26</sup> and  
 30 R<sup>27</sup> taken together and R<sup>28</sup> and R<sup>29</sup> taken together may each  
 form a heterocyclic group having five to seven ring members  
 including the nitrogen atom of said amino or amido radical,



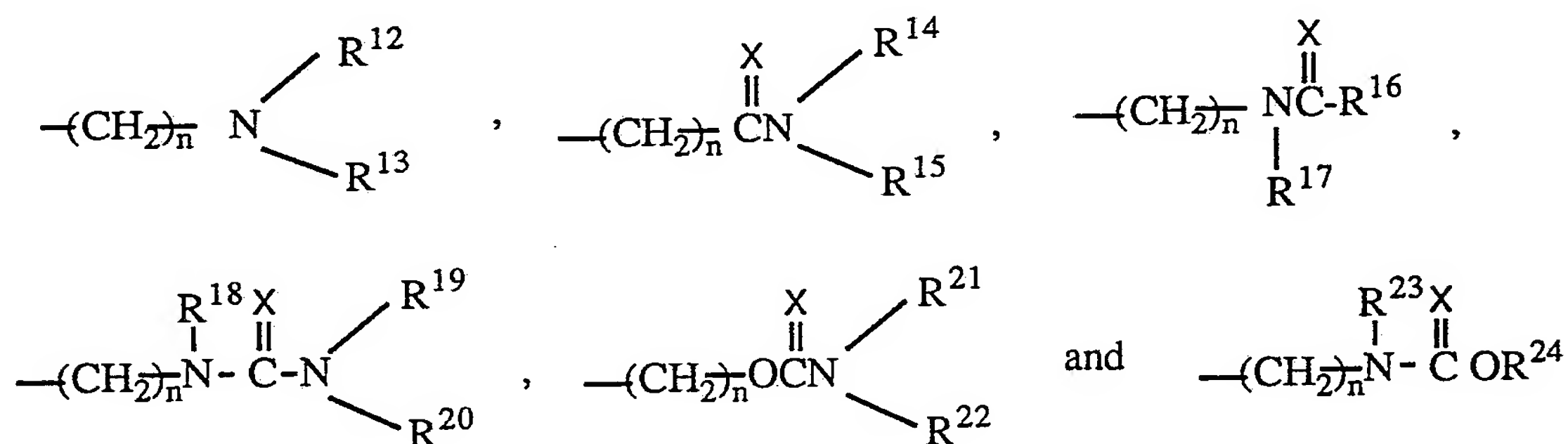
which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms and which heterocyclic group may be saturated or partially unsaturated; wherein R<sup>26</sup> and R<sup>27</sup> taken together and R<sup>31</sup> and R<sup>32</sup> taken together may each form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino or amido radical and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms;

with the proviso that at least one of said R<sup>1</sup> through R<sup>24</sup>, Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

6. Conjugate of Claim 5 wherein m is one; wherein each of R<sup>0</sup> through R<sup>11</sup> is independently selected from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, mercaptocarbonyl, mercaptothiocarbonyl, mercaptoalkyl, alkoxycarbonyloxy, alkylthio, cycloalkylthio, alkylthiocarbonyl, alkylcarbonylthio, alkylthiocarbonyloxy, alkylthiocarbonylthio, alkylthiothiocarbonyl, alkylthiothiocarbonylthio, arylthio, arylthiocarbonyl, arylcarbonylthio, arylthiocarbonyloxy, arylthiocarbonylthio, arylthiothiocarbonyl, arylthiothiocarbonylthio, aralkylthio, aralkylthiocarbonyl, aralkylcarbonylthio,

aralkylthiocarbonyloxy, aralkylthiocarbonylthio,  
 aralkylthiocarbonyl, aralkylthiocarbonylthio, mercapto,  
 alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl,  
 aralkylsulfonyl, arylsulfinyl, arylsulfonyl, phthalimido,  
 5 phthalimidoalkyl, heteroaryl, heteroarylalkyl,  
 cycloheteroalkyl, cycloheteroalkylalkyl and  
 cycloheteroalkylcarbonylalkyl wherein each of said  
 heteroaryl- and cycloheteroalkyl-containing groups has  
 one or more hetero ring atoms selected from oxygen, sulfur  
 10 and nitrogen atoms, and wherein each of  $R^0$  through  $R^{11}$  may  
 be further independently selected from amino and amido  
 radicals of the formula



15

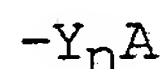
wherein X is selected from oxygen atom or sulfur atom;

wherein each n is a number independently selected from zero  
 20 to six, inclusive;

wherein each of  $R^{12}$  through  $R^{24}$  is independently selected  
 from hydrido, alkyl, cycloalkyl, cyano, amino,  
 monoalkylamino, dialkylamino, hydroxyalkyl,  
 25 cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl;

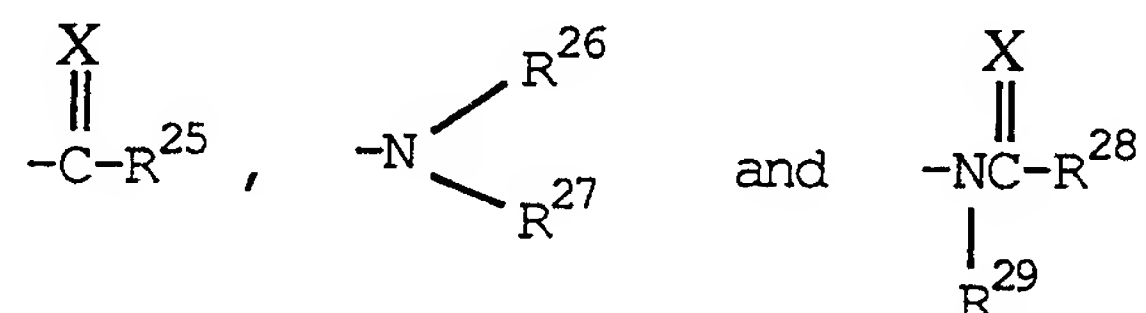
and wherein each of  $R^3$  through  $R^{11}$  may be further  
 independently selected from hydrido and haloalkyl, and from  
 acidic moieties of the formula

30

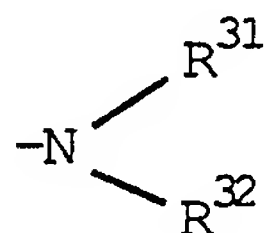


wherein n is a number selected from zero through three, inclusive; wherein A is an acidic group selected from acids containing one or more atoms selected from oxygen, sulfur, phosphorus and nitrogen atoms, and wherein said acidic group is selected to contain at least one acidic hydrogen atom, and the amide, ester and salt derivatives of said acidic moieties; wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aryl, aralkyl and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms;

and wherein any of the foregoing  $R^1$  through  $R^{24}$ , Y and A groups having a substitutable position may be substituted with one or more groups selected from alkyl, alkenyl, aralkyl, hydroxyalkyl, trifluoromethyl, difluoroalkyl, alkoxy, aryloxy, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxy carbonyl, carboxyl, mercaptocarbonyl, alkylthio, alkylthiocarbonyl, and amino and amido radicals of the formula

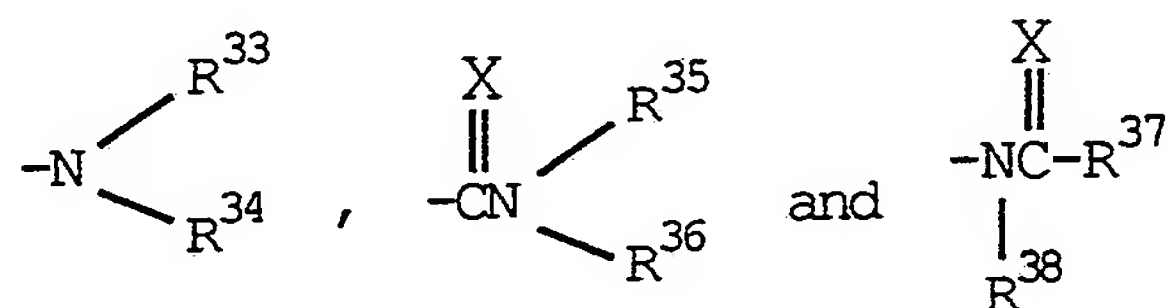


wherein X is selected from oxygen atom and sulfur atom; wherein  $R^{25}$  is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, and  $\text{DR}^{30}$  and



wherein D is selected from oxygen atom and sulfur atom, and  $R^{30}$  is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl and aryl; wherein each of  $R^{26}$ ,  $R^{27}$ ,  $R^{28}$ ,  $R^{29}$ ,  $R^{31}$  and  $R^{32}$  is independently selected from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl, haloalkyl,

cycloalkylalkyl, alkoxyalkyl, alkanoyl, alkoxycarbonyl,  
 carboxyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and  
 aryl, and wherein each of R<sup>26</sup>, R<sup>27</sup>, R<sup>28</sup>, R<sup>29</sup>, R<sup>31</sup> and R<sup>32</sup>  
 is further independently selected from amino and amido  
 radicals of the formula



wherein X is selected from oxygen atom or sulfur atom;

10

wherein each of R<sup>26</sup> through R<sup>31</sup> is independently selected  
 from hydrido, alkyl, cycloalkyl, cyano, amino,  
 monoalkylamino, dialkylamino, hydroxyalkyl,  
 cycloalkylalkyl, alkoxyalkyl, haloalkylsulfinyl,  
 haloalkylsulfonyl, aralkyl and aryl;

15

with the proviso that at least one of said R<sup>1</sup> through R<sup>24</sup>,  
 Y and A substituents contains a terminal primary or  
 secondary amino moiety or a moiety convertible to a primary  
 or secondary amino moiety;

20

or a tautomer thereof or a pharmaceutically-acceptable salt  
 thereof.

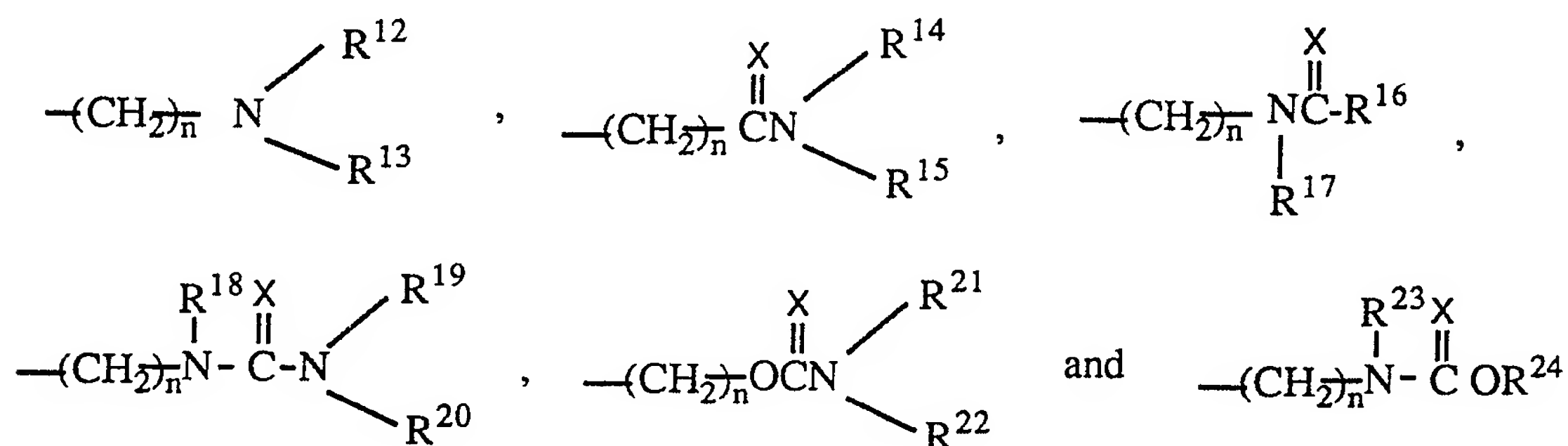
25

7. Conjugate of Claim 6 wherein m is one;  
 wherein each of R<sup>0</sup> through R<sup>11</sup> is independently selected  
 from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl,  
 cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl, aryloxy,  
 aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl,  
 alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl,  
 cycloalkynyl, cyano, nitro, carboxyl, carboxyalkyl,  
 alkylcarbonyloxy, mercaptocarbonyl, alkoxycarbonyloxy,  
 alkylcarbonyloxyalkyl, alkoxycarbonylalkyl,  
 aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, alkylthio,  
 cycloalkylthio, arylthio, aralkylthio,  
 aralkylthiocarbonylthio, mercapto, alkylsulfinyl,

35

alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl,  
 arylsulfinyl, arylsulfonyl, phthalimido, phthalimidoalkyl,  
 heteroaryl, heteroarylalkyl, cycloheteroalkyl,  
 cycloheteroalkylalkyl and cycloheteroalkylcarbonylalkyl  
 5 wherein each of said heteroaryl- and cycloheteroalkyl-  
 containing groups has one or more hetero ring atoms  
 selected from oxygen, sulfur and nitrogen atoms, and  
 wherein each of  $R^0$  through  $R^{11}$  may be further independently  
 selected from amino and amido radicals of the formula

10



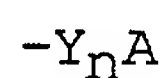
wherein X is selected from oxygen atom or sulfur atom;

15

wherein each n is a number independently selected from zero  
 to six, inclusive;

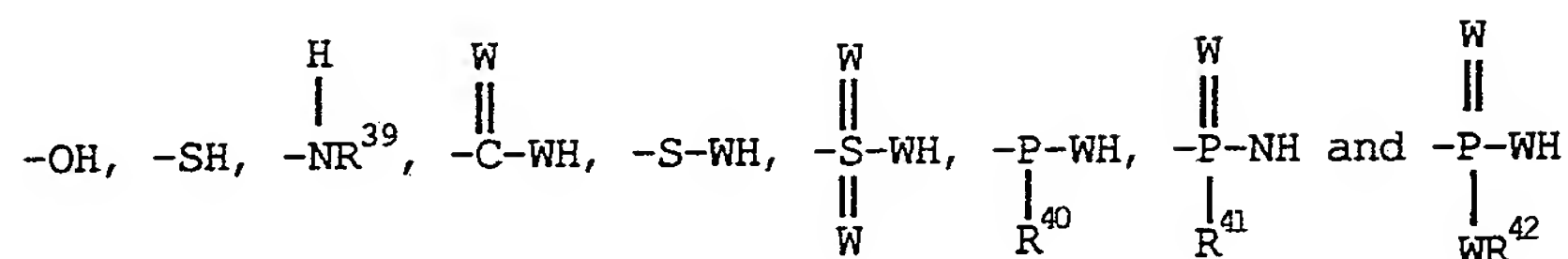
wherein each of  $R^{12}$  through  $R^{24}$  is independently selected  
 20 from hydrido, alkyl, cycloalkyl, cyano, amino,  
 monoalkylamino, dialkylamino, hydroxyalkyl,  
 cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl;

and wherein each of  $R^3$  through  $R^{11}$  may be an acidic moiety  
 25 further independently selected from hydrido and haloalkyl,  
 and from acidic moieties of the formula



30 wherein n is a number selected from zero through three,  
 inclusive;

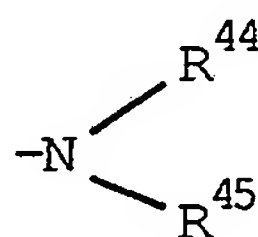
wherein A is selected from carboxylic acid and bioisosteres of carboxylic acid selected from



5

wherein each W is independently selected from oxygen atom, sulfur atom and  $\text{NR}^{43}$ ; wherein each of  $\text{R}^{39}$ ,  $\text{R}^{40}$ ,  $\text{R}^{41}$ ,  $\text{R}^{42}$  and  $\text{R}^{43}$  is independently selected from hydrido, alkyl, haloalkyl, haloalkylsulfonyl, haloalkylcarbonyl, cycloalkyl, cycloalkylalkyl, aryl and aralkyl; wherein each of  $\text{R}^{39}$ ,  $\text{R}^{40}$ ,  $\text{R}^{41}$  and  $\text{R}^{42}$  may be further independently selected from amino radicals of the formula

10



15

wherein each of  $\text{R}^{44}$  and  $\text{R}^{45}$  is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl, and wherein  $\text{R}^{44}$  and  $\text{R}^{45}$  taken together may form a heterocyclic group

20

having five to seven ring members including the nitrogen atom of said amino radical, which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms and which heterocyclic group may be saturated or partially

25

unsaturated; wherein  $\text{R}^{44}$  and  $\text{R}^{45}$  taken together may form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino radical and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen

30

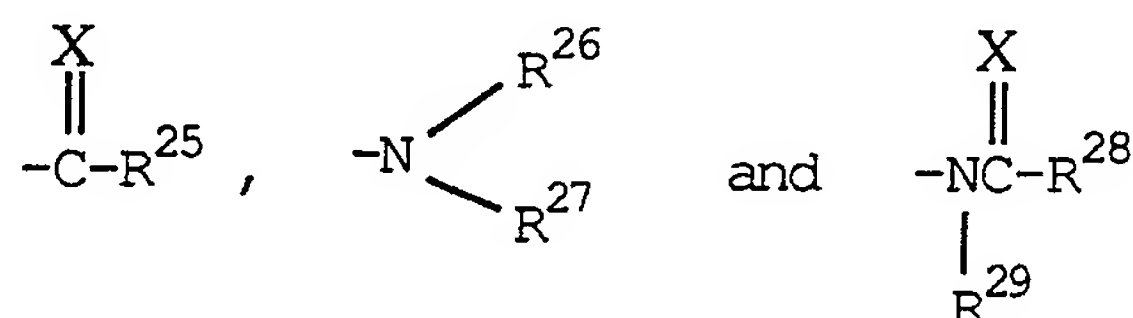
and sulfur atoms; wherein each of  $\text{R}^{40}$  and  $\text{R}^{41}$  may be further independently selected from hydroxy, alkoxy, alkylthio, aryloxy, arylthio, aralkylthio and aralkoxy; and the amide, ester and salt derivatives of said acidic groups;



wherein said bioisostere of carboxylic acid may be further selected from heterocyclic acidic groups consisting of heterocyclic rings of four to about nine ring members, which heterocyclic ring contains at least one hetero atom selected from oxygen, sulfur and nitrogen atoms, which heterocyclic ring may be saturated, fully unsaturated or partially unsaturated, and which heterocyclic ring may be attached at a single position selected from R<sup>3</sup> through R<sup>11</sup> or may be attached at any two adjacent positions selected from R<sup>3</sup> through R<sup>11</sup> so as to form a fused-ring system with one of the phenyl rings of the biphenyl moiety of Formula I; and the amide, ester and salt derivatives of said heterocyclic acidic groups;

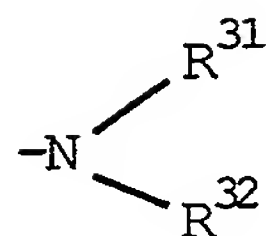
wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, aryl and aralkyl;

and wherein any of the foregoing R<sup>1</sup> through R<sup>24</sup>, Y and A groups having a substitutable position may be substituted by one or more groups selected from alkyl, difluoroalkyl, alkenyl, aralkyl, hydroxyalkyl, trifluoromethyl, alkoxy, aryloxy, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxy carbonyl, carboxyl, mercaptocarbonyl, alkylthio, alkylthiocarbonyl, and amino and amido radicals of the formula



wherein X is selected from oxygen atom and sulfur atom; wherein R<sup>25</sup> is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl and DR<sup>30</sup> and

292



wherein D is selected from oxygen atom and sulfur atom,  
 wherein R<sup>30</sup> is selected from hydrido, alkyl, cycloalkyl,  
 5 cycloalkylalkyl, aralkyl and aryl;

wherein each of R<sup>26</sup>, R<sup>27</sup>, R<sup>28</sup>, R<sup>29</sup>, R<sup>31</sup> and R<sup>32</sup> is  
 independently selected from hydrido, alkyl, cycloalkyl,  
 cyano, hydroxyalkyl, haloalkyl, cycloalkylalkyl,  
 10 alkoxyalkyl, alkanoyl, alkoxycarbonyl, carboxyl,  
 haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl;

with the proviso that at least one of said R<sup>1</sup> through R<sup>24</sup>,  
 Y and A substituents contains a terminal primary or  
 15 secondary amino moiety or a moiety convertible to a primary  
 or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt  
 thereof.

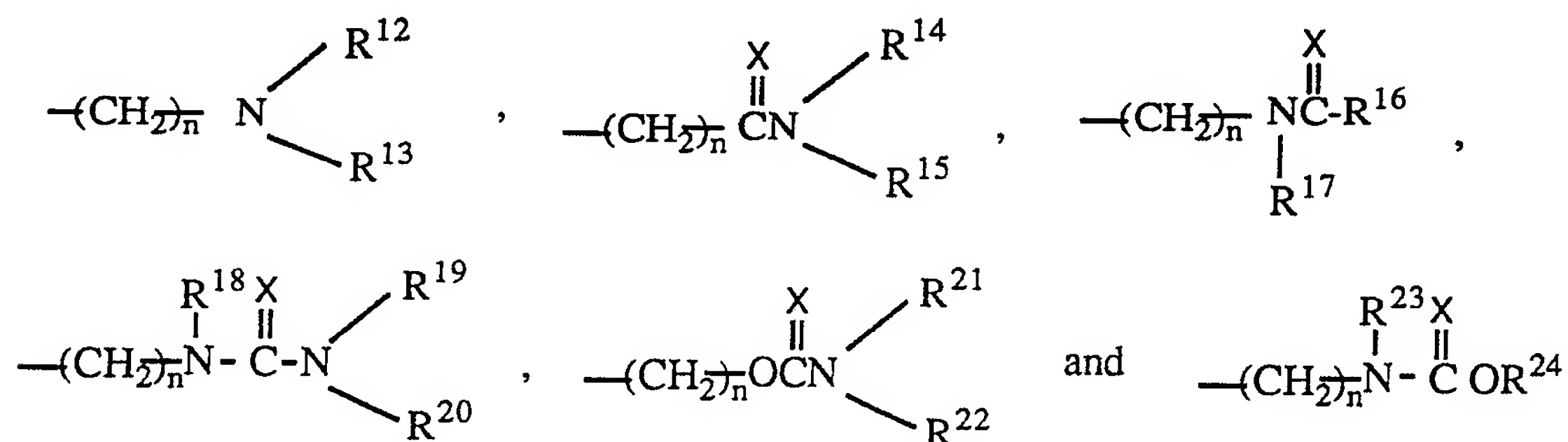
20

8. Conjugate of Claim 7 wherein m is one;  
 wherein each of R<sup>0</sup>, R<sup>1</sup> and R<sup>2</sup> is independently selected  
 from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl,  
 cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl, aryloxy,  
 25 aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl,  
 alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl,  
 cycloalkynyl, cyano, nitro, carboxyl, carboxyalkyl,  
 alkylcarbonyloxy, alkylcarbonyloxyalkyl,  
 alkoxycarbonylalkyl, aralkoxycarbonylalkyl,  
 30 aralkylcarbonyloxyalkyl, mercaptocarbonyl, mercaptoalkyl,  
 alkoxycarbonyloxy, alkylthio, cycloalkylthio, arylthio,  
 aralkylthio, mercapto, alkylsulfinyl, alkylsulfonyl,  
 aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl,  
 arylsulfonyl, phthalimido, phthalimidoalkyl, heteroaryl,  
 35 heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl

**SUBSTITUTE SHEET**



and cycloheteroalkylcarbonylalkyl wherein each of said heteroaryl- and cycloheteroalkyl-containing groups has one or more hetero ring atoms selected from oxygen, sulfur and nitrogen atoms, and wherein each of R<sup>0</sup> through R<sup>11</sup> may be further independently selected from amino and amido radicals of the formula



10

wherein X is selected from oxygen atom and sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

15

wherein each of R<sup>12</sup> through R<sup>24</sup> is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl;

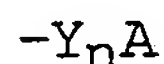
20

wherein each of R<sup>3</sup> through R<sup>11</sup> is independently selected from hydrido, hydroxy, alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxy carbonyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, cyano, nitro, carboxyl, alkylthio, aralkylthio, mercapto, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms;

30

294

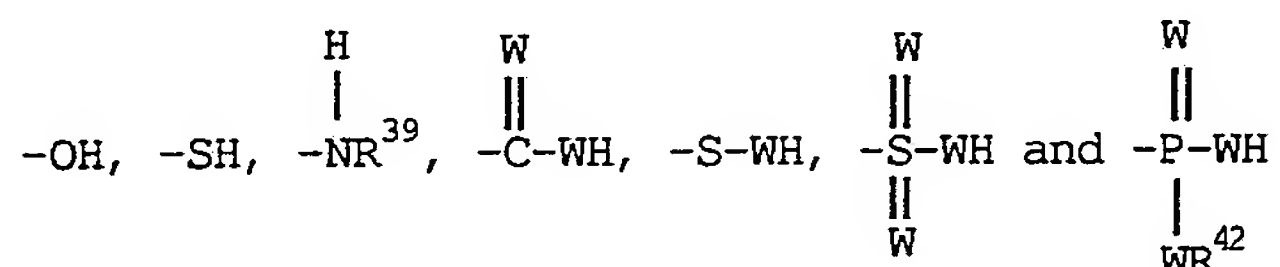
and wherein each of  $R^3$  through  $R^{11}$  may be an acidic moiety further independently selected from acidic moieties of the formula



5

wherein  $n$  is a number selected from zero through three, inclusive; wherein  $A$  is selected from carboxylic acid and bioisosteres of carboxylic acid selected from

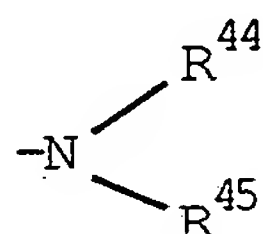
10



15

wherein each  $W$  is independently selected from oxygen atom, sulfur atom and  $NR^{43}$ ; wherein each of  $R^{39}$ ,  $R^{42}$  and  $R^{43}$  is independently selected from hydrido, alkyl, haloalkyl, haloalkylsulfonyl, haloalkylcarbonyl, cycloalkyl, cycloalkylalkyl, aryl and aralkyl; wherein each of  $R^{39}$  and  $R^{42}$  may be further independently selected from amino radical of the formula

20



25

30

35

wherein each of  $R^{44}$  and  $R^{45}$  is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl, and wherein  $R^{44}$  and  $R^{45}$  taken together may form a heterocyclic group having five to seven ring members including the nitrogen atom of said amino radical, which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms, and which heterocyclic group may be saturated or partially unsaturated; wherein  $R^{44}$  and  $R^{45}$  taken together may form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino radical and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen

**SUBSTITUTE SHEET**

and sulfur atoms; and the amide, ester and salt derivatives of said acidic groups; wherein said bioisostere of carboxylic acid may be further selected from heterocyclic acidic groups consisting of heterocyclic rings of four to about nine ring members, which ring contains at least one hetero atom, selected from oxygen, sulfur and nitrogen atoms, which heterocyclic ring may be saturated, fully unsaturated or partially unsaturated, and which heterocyclic ring may be attached at a single position selected from  $R^3$  through  $R^{11}$  or may be attached at any two adjacent positions selected from  $R^3$  through  $R^{11}$  so as to form a fused-ring system with one of the phenyl rings of Formula I; and the amide, ester and salt derivatives of said heterocyclic acidic groups;

wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, aryl and aralkyl;

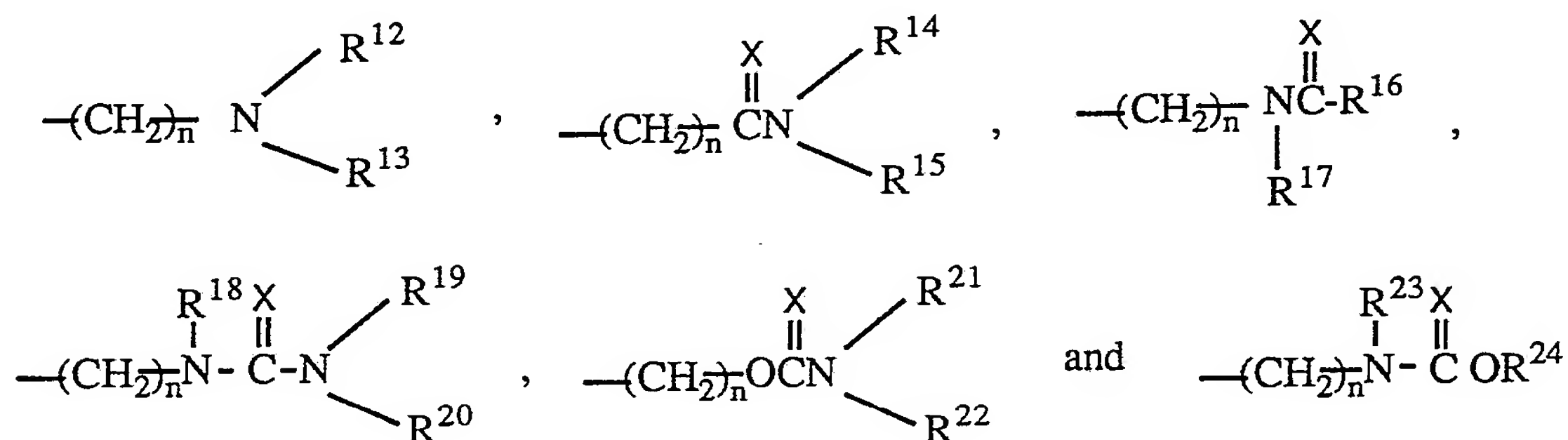
wherein each of  $R^1$  through  $R^{24}$ , Y and A independently may be substituted at any substitutable position with one or more groups selected from alkyl, cycloalkyl, cycloalkylalkyl, hydroxy, oxo, trifluoromethyl, difluoroalkyl, alkoxycarbonyl, cyano, nitro, alkylsulfonyl, haloalkylsulfonyl, aryl, aralkyl, alkoxy, aryloxy and aralkoxy;

with the proviso that at least one of said  $R^1$  through  $R^{24}$ , Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

9. Conjugate of Claim 8 wherein m is one; wherein each of  $R^0$ ,  $R^1$  and  $R^2$  is independently selected from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl,

cycloalkylalkyl, alkoxy, aralkyl, aryl, benzoyl, phenoxy,  
 phenoxyalkyl, phenalkyloxy, phenylthio, phenalkylthio,  
 aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl,  
 alkenyl, cycloalkenyl, alkynyl, cyano, nitro, carboxyl,  
 5 carboxyalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl,  
 alkoxycarbonylalkyl, aralkoxycarbonylalkyl,  
 aralkylcarbonyloxyalkyl, mercaptocarbonyl, mercaptoalkyl,  
 alkoxycarbonyloxy, alkylthio, cycloalkylthio, phthalimido,  
 phthalimidoalkyl, heteroaryl, heteroarylalkyl,  
 10 cycloheteroalkyl, cycloheteroalkylalkyl and  
 cycloheteroalkylcarbonylalkyl wherein each of said  
 heteroaryl- and cycloheteroalkyl-containing groups has one  
 or more hetero ring atoms selected from oxygen, sulfur and  
 nitrogen atoms, and wherein each of R<sup>0</sup> through R<sup>11</sup> may be  
 15 further independently selected from amino and amido  
 radicals of the formula



20

wherein X is selected from oxygen atom and sulfur atom;

wherein each n is a number independently selected from zero  
 to six, inclusive;

25

wherein each of R<sup>12</sup> through R<sup>24</sup> is independently selected  
 from hydrido, alkyl, cycloalkyl, cyano, amino,  
 hydroxyalkyl, alkoxyalkyl, phenalkyl and phenyl;

30

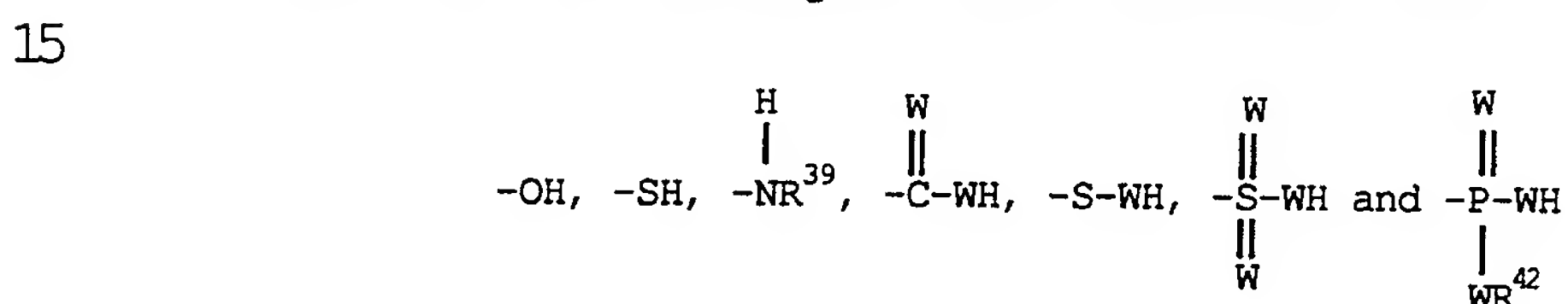
wherein each of R<sup>3</sup> through R<sup>11</sup> is independently selected  
 from hydrido, hydroxy, alkyl, hydroxyalkyl, halo,  
 haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, phenalkyl,

phenyl, benzoyl, phenoxy, phenalkyloxy, alkoxyalkyl,  
alkylcarbonyl, alkoxycarbonyl, alkenyl, cyano, nitro,  
carboxyl, alkylthio, mercapto and heteroaryl having one or  
more ring atoms selected from oxygen, sulfur and nitrogen  
atoms;

and wherein each of  $R^3$  through  $R^{11}$  may be an acidic moiety  
further independently selected from acidic moieties of the  
formula



wherein n is a number selected from zero through two,  
inclusive; wherein A is selected from carboxylic acid and  
bioisosteres of carboxylic acid selected from



wherein each W is independently selected from oxygen atom,  
sulfur atom and  $NR^{43}$ ; wherein each of  $R^{39}$ ,  $R^{42}$  and  $R^{43}$  is  
independently selected from hydrido, alkyl, haloalkyl,  
haloalkylsulfonyl, haloalkylcarbonyl, cycloalkyl, phenyl  
and benzyl; wherein each of  $R^{39}$  and  $R^{42}$  may be further  
independently selected from amino radical of the formula



wherein each of  $R^{44}$  and  $R^{45}$  is independently selected from  
hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl,  
alkoxyalkyl, benzyl and phenyl; and the amide, ester and  
salt derivatives of said acidic groups;

wherein said bioisostere of carboxylic acid may be further  
selected from heterocyclic acidic groups consisting of  
heterocyclic rings of four to about nine ring members,  
which ring contains at least one hetero atom, selected from

oxygen, sulfur and nitrogen atoms, which heterocyclic ring may be saturated, fully unsaturated or partially unsaturated, and which heterocyclic ring may be attached at a single position selected from  $R^3$  through  $R^{11}$  or may be  
5 attached at any two adjacent positions selected from  $R^3$  through  $R^{11}$  so as to form a fused-ring system with one of the phenyl rings of the biphenyl moiety of Formula I; and the amide, ester and salt derivatives of said heterocyclic acidic groups;

10

wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, phenyl, phenalkyl and aralkyl;

15

wherein each of  $R^1$  through  $R^{24}$ , Y and A and independently may be substituted at any substitutable position with one or more groups selected from alkyl, cycloalkyl, cycloalkylalkyl, hydroxy, oxo, trifluoromethyl, difluoroalkyl, alkoxycarbonyl, cyano, nitro, alkylsulfonyl,  
20 haloalkylsulfonyl, aryl, aralkyl, alkoxy, aryloxy and aralkoxy;

25

with the proviso that at least one of said  $R^1$  through  $R^{24}$ , Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

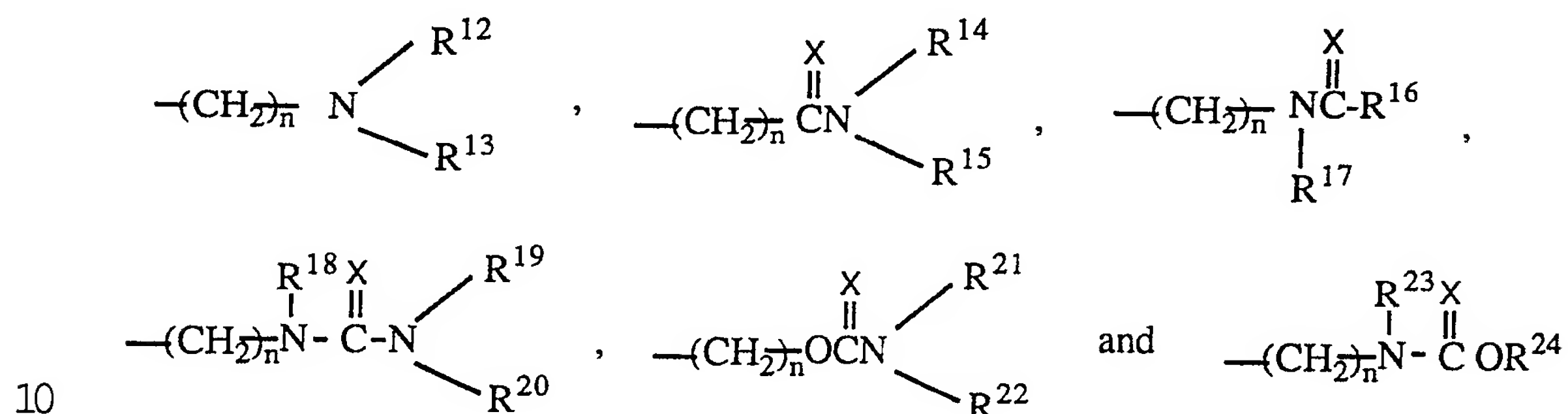
30

10. Conjugate of Claim 9 wherein m is one; wherein  $R^0$  is selected from alkyl, alkenyl, phenyl, alkylthio, cycloalkyl, cycloalkylalkyl and cycloalkylthio; wherein each of  $R^1$  and  $R^2$  is independently selected from  
35 alkyl, aminoalkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, benzoyl, phenoxy, phenoxyalkyl, phenalkyloxy, phenylthio, phenalkylthio, aralkoxy, alkoxyalkyl, acetyl,

**SUBSTITUTE SHEET**



alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cyano,  
 nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy,  
 mercaptoalkyl, mercaptocarbonyl, alkoxycarbonyloxy,  
 alkylcarbonyloxyalkyl, alkoxycarbonylalkyl,  
 5 aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl,  
 phthalimido, phthalimidoalkyl, imidazoalkyl, tetrazole,  
 tetrazolealkyl, alkylthio, cycloalkylthio, and amino and  
 amido radicals of the formula



wherein X is selected from oxygen atom and sulfur atom;

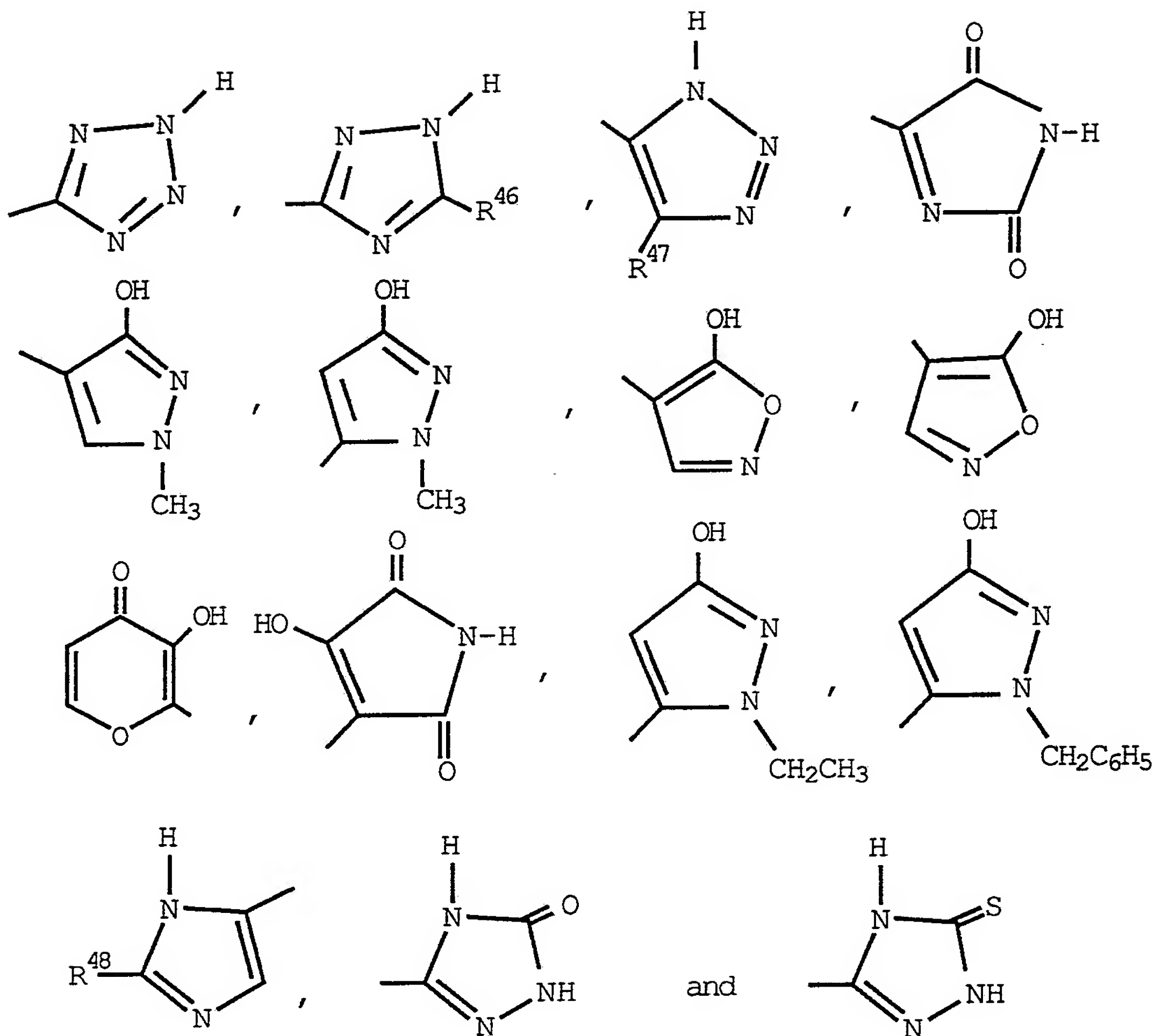
wherein each n is a number independently selected from zero  
 15 to six, inclusive;

wherein each of R<sup>12</sup> through R<sup>24</sup> is independently selected  
 from hydrido, alkyl, cycloalkyl, cyano, amino,  
 hydroxyalkyl, alkoxyalkyl, phenalkyl and phenyl;

wherein each of R<sup>3</sup> through R<sup>11</sup> is independently selected  
 from hydrido, hydroxy, alkyl, hydroxyalkyl, halo,  
 haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, phenalkyl,  
 phenyl, benzoyl, phenoxy, phenalkyloxy, alkoxyalkyl,  
 25 acetyl, alkoxycarbonyl, alkenyl, cyano, nitro, carboxyl,  
 alkylthio and mercapto;

and wherein each of R<sup>3</sup> through R<sup>11</sup> may be an acidic moiety  
 further independently selected from acidic moieties  
 30 consisting of CO<sub>2</sub>H, CO<sub>2</sub>CH<sub>3</sub>, SH, CH<sub>2</sub>SH, C<sub>2</sub>H<sub>4</sub>SH, PO<sub>3</sub>H<sub>2</sub>,  
 NHSO<sub>2</sub>CF<sub>3</sub>, NHSO<sub>2</sub>C<sub>6</sub>F<sub>5</sub>, SO<sub>3</sub>H, CONHNH<sub>2</sub>, CONHNHSO<sub>2</sub>CF<sub>3</sub>, CONHOCH<sub>3</sub>,  
 CONHOC<sub>2</sub>H<sub>5</sub>, CONHCF<sub>3</sub>, OH, CH<sub>2</sub>OH, C<sub>2</sub>H<sub>4</sub>CH, OPO<sub>3</sub>H<sub>2</sub>, OSO<sub>3</sub>H,

300



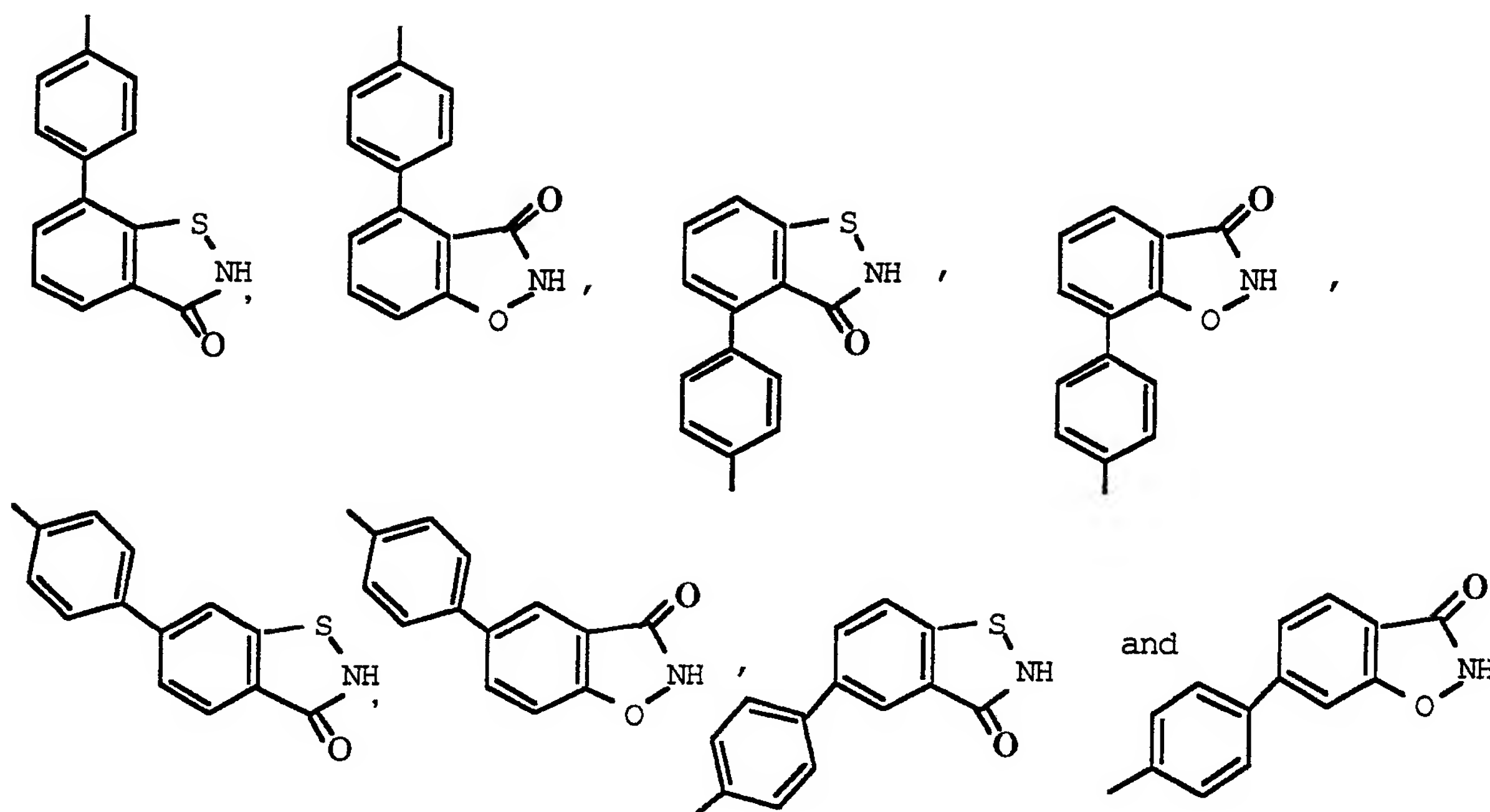
- 5 wherein each of  $R^{46}$ ,  $R^{47}$  and  $R^{48}$  is independently selected from H, Cl, CN,  $NO_2$ ,  $CF_3$ ,  $C_2F_5$ ,  $C_3F_7$ ,  $CHF_2$ ,  $CH_2F$ ,  $CO_2CH_3$ ,  $CO_2C_2H_5$ ,  $SO_2CH_3$ ,  $SO_2CF_3$  and  $SO_2C_6H_5$ ; wherein Z is selected from O, S,  $NR^{49}$  and  $CH_2$ ; wherein  $R^{49}$  is selected from hydrido,  $CH_3$  and  $CH_2C_6H_5$ ; and wherein said acidic moiety
- 10 may be a heterocyclic acidic group attached at any two adjacent positions of  $R^3$  through  $R^{11}$  so as to form a fused ring system so as to include one of the phenyl rings of the biphenyl moiety of Formula I, said biphenyl fused ring system selected from

15

**SUBSTITUTE SHEET**






301



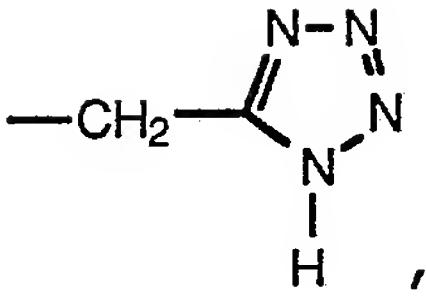

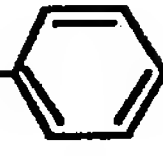

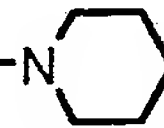
and the esters, amides and salts of said acidic moieties;

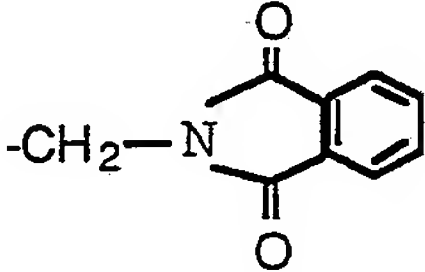

- 5 with the proviso that at least one of said  $R^1$  through  $R^{24}$  substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;
- 10 or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

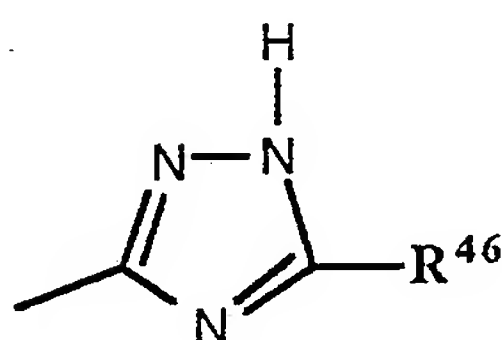
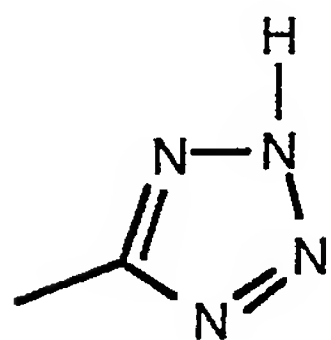
11. Conjugate of Claim 10 wherein m is one; wherein  $R^0$  is selected from  $C_4H_9(n)$ ,  $CH_3CH_2CH=CH$ ,  $C_3H_7(N)$ ,  $SC_3H_7$ , , ,  $C_2H_5$ ,  $C_5H_{11}(n)$ ,  $C_6H_{13}(n)$ ,  $SC_4H_9$ , ,  $CH_3CH=CH$  and  $CH_3CH_2CH_2CH=CH-$ ; wherein each of  $R^1$  and  $R^2$  is independently selected from amino, aminomethyl, aminoethyl, aminopropyl,  $CH_2OH$ ,  $CH_2OCOCH_3$ ,  $CH_2Cl$ ,  $Cl$ ,  $CH_2OCH_3$ ,  $CH_2OCH(CH_3)_2$ ,  $I$ ,  $CHO$ ,

**SUBSTITUTE SHEET**

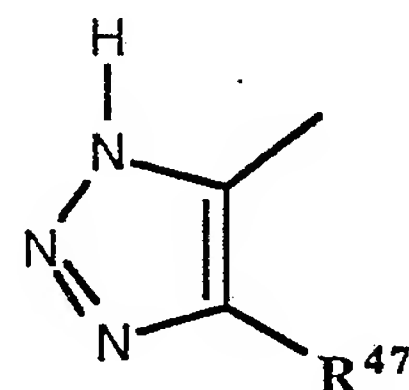
302

$\text{CH}_2\text{CO}_2\text{H}$ ,  $\text{CH}(\text{CH}_3)\text{CO}_2\text{H}$ ,  $\text{NO}_2$ ,  $\text{Cl}$ ,  
  
 $-\text{CH}_2\text{OCOCH}_2\text{CH}_2-$  ,  $-\text{CO}_2\text{CH}_3$ ,  $-\text{CONH}_2$ ,  $-\text{CONHCH}_3$ ,  $\text{CON}(\text{CH}_3)_2$ ,  
 $-\text{CH}_2-\text{NHCO}_2\text{C}_2\text{H}_5$ ,  $-\text{CH}_2\text{NHCO}_2-$  ,  $-\text{CH}_2\text{NHCO}_2\text{CH}_3$ ,  $-\text{CH}_2\text{NHCO}_2\text{C}_3\text{H}_7$ ,  
 $-\text{CH}_2\text{NHCO}_2\text{CH}_2(\text{CH}_3)_2$ ,  $-\text{CH}_2\text{NHCO}_2\text{C}_4\text{H}_9$ ,  $\text{CH}_2\text{NHCO}_2$ -adamantyl,  
5  $-\text{CH}_2\text{NHCO}_2$ -(1-naphthyl),  $-\text{CH}_2\text{NHCONHCH}_3$ ,  $-\text{CH}_2\text{NHCONHC}_2\text{H}_5$ ,  
 $-\text{CH}_2\text{NHCONHC}_3\text{H}_7$ ,  $-\text{CH}_2\text{NHCONHC}_4\text{H}_9$ ,  $-\text{CH}_2\text{NHCONHCH}(\text{CH}_3)_2$ ,  
 $-\text{CH}_2\text{NHCONH}$ (1-naphthyl),  $-\text{CH}_2\text{NHCONH}$ (1-adamantyl),  $\text{CO}_2\text{H}$ ,  
 $-\text{CH}_2\text{CH}_2-\text{CO}-\text{N}$  ,  $-\text{CH}_2\text{CH}_2\text{CO}-\text{N}$  ,  $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$ ,  
 $-\text{CH}_2\text{CH}_2\text{F}$ ,  $-\text{CH}_2\text{OCONHCH}_3$ ,  $-\text{CH}_2\text{OCSNHCH}_3$ ,  $-\text{CH}_2\text{NHCSOC}_3\text{H}_7$ ,

10  $-\text{CH}_2\text{CH}_2\text{CH}_2\text{F}$ ,  $-\text{CH}_2\text{ONO}_2$ ,  
,  $-\text{CH}_2\text{SH}$ ,  $-\text{CH}_2\text{O}-$  ,  
 12.  $\text{Cl}$ ,  $\text{NO}_2$ ,  $\text{CF}_3$ ,  $\text{CH}_2\text{OH}$ ,  $\text{Br}$ ,  $\text{F}$ ,  $\text{I}$ , methyl, ethyl, n-propyl,  
 isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-  
 pentyl, isopentyl, neopentyl, phenyl, benzyl, phenethyl,  
 cyclohexyl, cyclohexylmethyl, 1-oxoethyl, 1-oxopropyl, 1-  
 15 oxobutyl, 1-oxopentyl, 1,1-dimethoxypropyl, 1,1-  
 dimethoxybutyl, 1,1-dimethoxypentyl, hydroxyalkyl, halo,  
 difluoromethyl, 1,1-difluoroethyl, 1,1-difluoropropyl, 1,1-  
 difluorobutyl and 1,1-difluoropentyl; wherein each of  $\text{R}^3$   
 through  $\text{R}^{11}$  is hydrido, with the proviso that at least one  
 20 of  $\text{R}^5$ ,  $\text{R}^6$ ,  $\text{R}^8$  and  $\text{R}^9$  is an acidic group selected from  $\text{CO}_2\text{H}$ ,  
 $\text{SH}$ ,  $\text{PO}_3\text{H}_2$ ,  $\text{SO}_3\text{H}$ ,  $\text{CONHNH}_2$ ,  $\text{CONHNHSO}_2\text{CF}_3$ ,  $\text{OH}$ ,



and



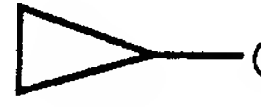

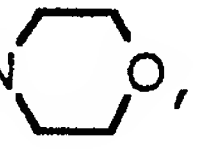



25 wherein each of  $\text{R}^{46}$  and  $\text{R}^{47}$  is independently selected from  
 $\text{Cl}$ ,  $\text{CN}$ ,  $\text{NO}_2$ ,  $\text{CF}_3$ ,  $\text{CO}_2\text{CH}_3$  and  $\text{SO}_2\text{CF}_3$ ;

SUBSTITUTE SHEET

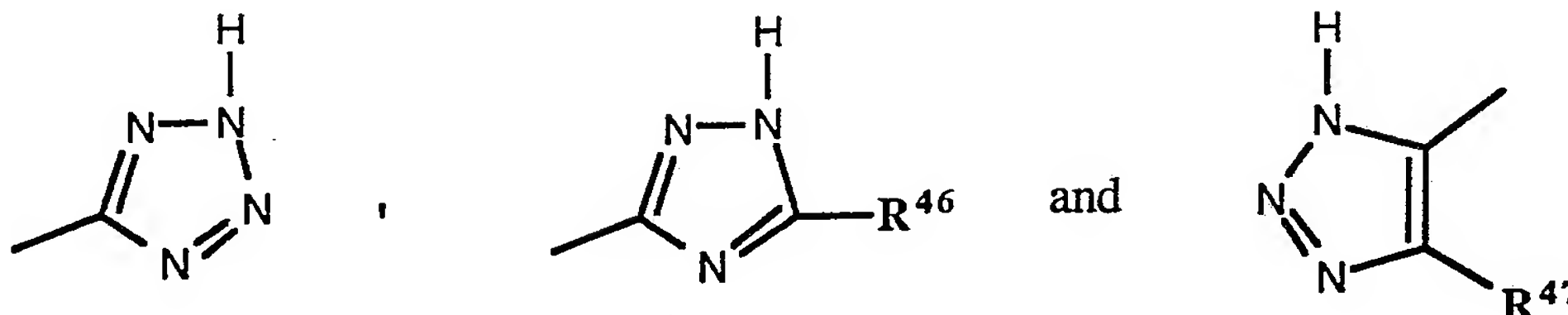
with the proviso that at least one of said  $R^1$  through  $R^{11}$  substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

12. Conjugate of Claim 11 wherein m is one; wherein  $R^0$  is selected from  $C_4H_9(n)$ ,  $CH_3CH_2CH=CH$ ,  $C_3H_7(N)$ ,  $SC_3H_7$ , , ,  $C_2H_5$ ,  $C_5H_{11}(n)$ ,  $C_6H_{13}(n)$ ,  $SC_4H_9$ , ,  $CH_3CH=CH$  and  $CH_3CH_2CH_2CH=CH-$ ; wherein  $R^1$  is selected from amino, aminomethyl, aminoethyl, aminopropyl,  $CH_2OH$ ,  $CH_2OCOCH_3$ ,  $CH_2Cl$ ,  $Cl$ ,  $CH_2OCH_3$ ,  $CH_2OCH(CH_3)_2$ ,  $I$ ,  $CHO$ ,  $CH_2CO_2H$ ,  $CH(CH_3)CO_2H$ ,  $-CO_2CH_3$ ,  $-CONH_2$ ,  $-CONHCH_3$ ,  $CON(CH_3)_2$ ,  $-CH_2-NHCO_2C_2H_5$ ,  $-CH_2NHCO_2-$ ,  $-CH_2NHCO_2CH_3$ ,  $-CH_2NHCO_2C_3H_7$ ,  $-CH_2NHCO_2CH_2(CH_3)_2$ ,  $-CH_2NHCO_2C_4H_9$ ,  $CH_2NHCO_2$ -adamantyl,  $-CH_2NHCO_2$ -(1-naphthyl),  $-CH_2NHCONHCH_3$ ,  $-CH_2NHCONHC_2H_5$ ,  $-CH_2NHCONHC_3H_7$ ,  $-CH_2NHCONHC_4H_9$ ,  $-CH_2NHCONHCH(CH_3)_2$ ,  $-CH_2NHCONH$ (1-naphthyl),  $-CH_2NHCONH$ (1-adamantyl),  $CO_2H$ ,  $-CH_2CH_2-CO-N$ ,  $-CH_2CH_2CH_2CO_2H$ ,  $-CH_2CH_2F$ ,  $-CH_2OCONHCH_3$ ,  $-CH_2CH_2CH_2F$ ,  $-CH_2SH$  and  $-CH_2O-$ ;
- wherein  $R^2$  is selected from  $H$ ,  $Cl$ ,  $NO_2$ ,  $CF_3$ ,  $CH_2OH$ ,  $Br$ ,  $F$ ,  $I$ , methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, neopentyl, phenyl, benzyl, phenethyl, cyclohexyl, cyclohexylmethyl, 1-oxoethyl, 1-oxopropyl, 1-oxobutyl, 1-oxopentyl, 1,1-dimethoxypropyl, 1,1-dimethoxybutyl, 1,1-dimethoxypentyl, hydroxyalkyl, halo, difluoromethyl, 1,1-difluoroethyl, 1,1-difluoropropyl, 1,1-difluorobutyl and 1,1-difluoropentyl; wherein each of  $R^3$  through  $R^{11}$  is hydrido, with the proviso that at least one of  $R^5$ ,  $R^6$ ,  $R^8$  and  $R^9$  is an acidic group

304

selected from  $\text{CO}_2\text{H}$ ,  $\text{SH}$ ,  $\text{PO}_3\text{H}_2$ ,  $\text{SO}_3\text{H}$ ,  $\text{CONHNH}_2$ ,  $\text{CONHNHSO}_2\text{CF}_3$ ,  $\text{OH}$ ,



5

wherein each of  $\text{R}^{46}$  and  $\text{R}^{47}$  is independently selected from  $\text{Cl}$ ,  $\text{CN}$ ,  $\text{NO}_2$ ,  $\text{CF}_3$ ,  $\text{CO}_2\text{CH}_3$  and  $\text{SO}_2\text{CF}_3$ ;

10 with the proviso that at least one of said  $\text{R}^1$  through  $\text{R}^{11}$  substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

15 or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

13. Conjugate of Claim 11 wherein  $m$  is one; wherein  $\text{R}^0$  is selected from  $\text{C}_4\text{H}_9(n)$ ,  $\text{CH}_3\text{CH}_2\text{CH}=\text{CH}$ ,  $\text{C}_3\text{H}_7(\text{N})$ ,

$\text{SC}_3\text{H}_7$ , , ,  $\text{C}_2\text{H}_5$ ,  $\text{C}_5\text{H}_{11}(n)$ ,  $\text{C}_6\text{H}_{13}(n)$ ,




20  $\text{SC}_4\text{H}_9$ ,   $\text{CH}_2\text{S}$ ,  $\text{CH}_3\text{CH}=\text{CH}$  and  $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}=\text{CH}-$ ;

wherein  $\text{R}^1$  is selected from  $\text{H}$ ,  $\text{Cl}$ ,  $\text{NO}_2$ ,  $\text{CF}_3$ ,  $\text{CH}_2\text{OH}$ ,  $\text{Br}$ ,  $\text{F}$ ,  $\text{I}$ , methyl, ethyl,  $n$ -propyl, isopropyl,  $n$ -butyl, sec-butyl, isobutyl, tert-butyl,  $n$ -pentyl, isopentyl, neopentyl, phenyl, benzyl, phenethyl, cyclohexyl, cyclohexylmethyl, 1-oxoethyl, 1-oxopropyl, 1-oxobutyl, 1-oxopentyl, 1,1-dimethoxypropyl, 1,1-dimethoxybutyl, 1,1-dimethoxypentyl, hydroxyalkyl, halo, difluoromethyl, 1,1-difluoroethyl, 1,1-difluoropropyl, 1,1-difluorobutyl and 1,1-difluoropentyl;

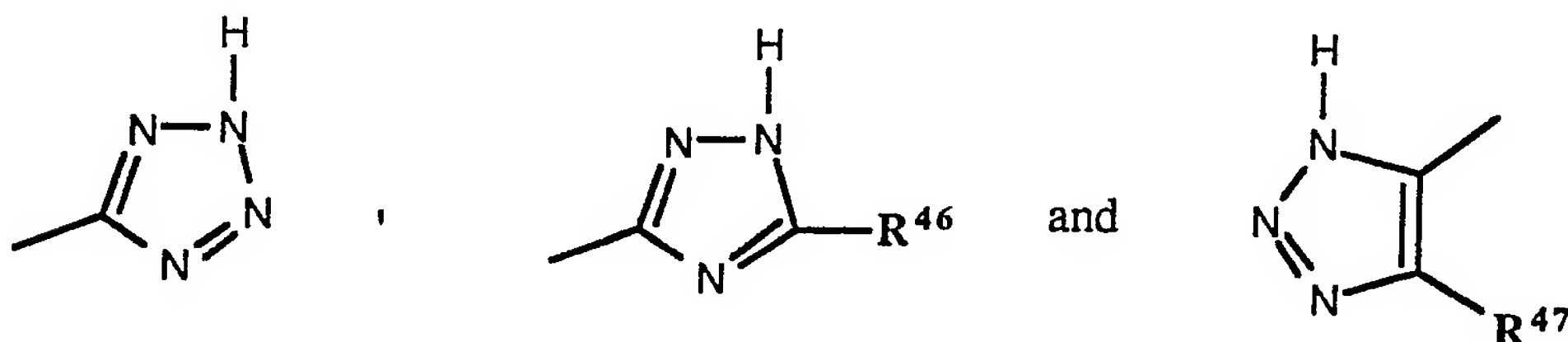
25 wherein  $\text{R}^2$  is selected from amino, aminomethyl, aminoethyl, aminopropyl,  $\text{CH}_2\text{OH}$ ,  $\text{CH}_2\text{OCOCH}_3$ ,  $\text{CH}_2\text{Cl}$ ,  $\text{Cl}$ ,  $\text{CH}_2\text{OCH}_3$ ,  $\text{CH}_2\text{OCH}(\text{CH}_3)_2$ ,  $\text{I}$ ,  $\text{CHO}$ ,  $\text{CH}_2\text{CO}_2\text{H}$ ,  $\text{CH}(\text{CH}_3)\text{CO}_2\text{H}$ ,  $-\text{CO}_2\text{CH}_3$ ,  $-\text{CONH}_2$ ,  $-\text{CONHCH}_3$ ,  $\text{CON}(\text{CH}_3)_2$ ,

**SUBSTITUTE SHEET**

305

$-\text{CH}_2-\text{NHCO}_2\text{C}_2\text{H}_5$ ,  $-\text{CH}_2\text{NHCO}_2-$ ,  $-\text{CH}_2\text{NHCO}_2\text{CH}_3$ ,  $-\text{CH}_2\text{NHCO}_2\text{C}_3\text{H}_7$ ,  
 $-\text{CH}_2\text{NHCO}_2\text{CH}_2(\text{CH}_3)_2$ ,  $-\text{CH}_2\text{NHCO}_2\text{C}_4\text{H}_9$ ,  $\text{CH}_2\text{NHCO}_2$ -adamantyl,  
 $-\text{CH}_2\text{NHCO}_2$ -(1-naphthyl),  $-\text{CH}_2\text{NHCONHCH}_3$ ,  $-\text{CH}_2\text{NHCONHC}_2\text{H}_5$ ,  
 $-\text{CH}_2\text{NHCONHC}_3\text{H}_7$ ,  $-\text{CH}_2\text{NHCONHC}_4\text{H}_9$ ,  $-\text{CH}_2\text{NHCONHCH}(\text{CH}_3)_2$ ,  
 5  $-\text{CH}_2\text{NHCONH}(1\text{-naphthyl})$ ,  $-\text{CH}_2\text{NHCONH}(1\text{-adamantyl})$ ,  $\text{CO}_2\text{H}$ ,  
 $-\text{CH}_2\text{CH}_2\text{CO}-\text{N}$ ,  $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$ ,  $-\text{CH}_2\text{CH}_2\text{F}$ ,  $-\text{CH}_2\text{OCONHCH}_3$ , -  
 $\text{CH}_2\text{CH}_2\text{CH}_2\text{F}$ ,  $-\text{CH}_2\text{SH}$  and  $-\text{CH}_2\text{O}-$ ;

wherein each of  $\text{R}^3$  through  $\text{R}^{11}$  is hydrido, with the proviso  
 that at least one of  $\text{R}^5$ ,  $\text{R}^6$ ,  $\text{R}^8$  and  $\text{R}^9$  is an acidic group  
 10 selected from  $\text{CO}_2\text{H}$ ,  $\text{SH}$ ,  $\text{PO}_3\text{H}_2$ ,  $\text{SO}_3\text{H}$ ,  $\text{CONHNH}_2$ ,  $\text{CONHNHSO}_2\text{CF}_3$ ,  
 $\text{OH}$ ,



15 wherein each of  $\text{R}^{46}$  and  $\text{R}^{47}$  is independently selected from  
 $\text{Cl}$ ,  $\text{CN}$ ,  $\text{NO}_2$ ,  $\text{CF}_3$ ,  $\text{CO}_2\text{CH}_3$  and  $\text{SO}_2\text{CF}_3$ ;

with the proviso that at least one of said  $\text{R}^1$  through  $\text{R}^{11}$   
 substituents contains a terminal primary or secondary amino  
 20 moiety or a moiety convertible to a primary or secondary  
 amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt  
 thereof.

25

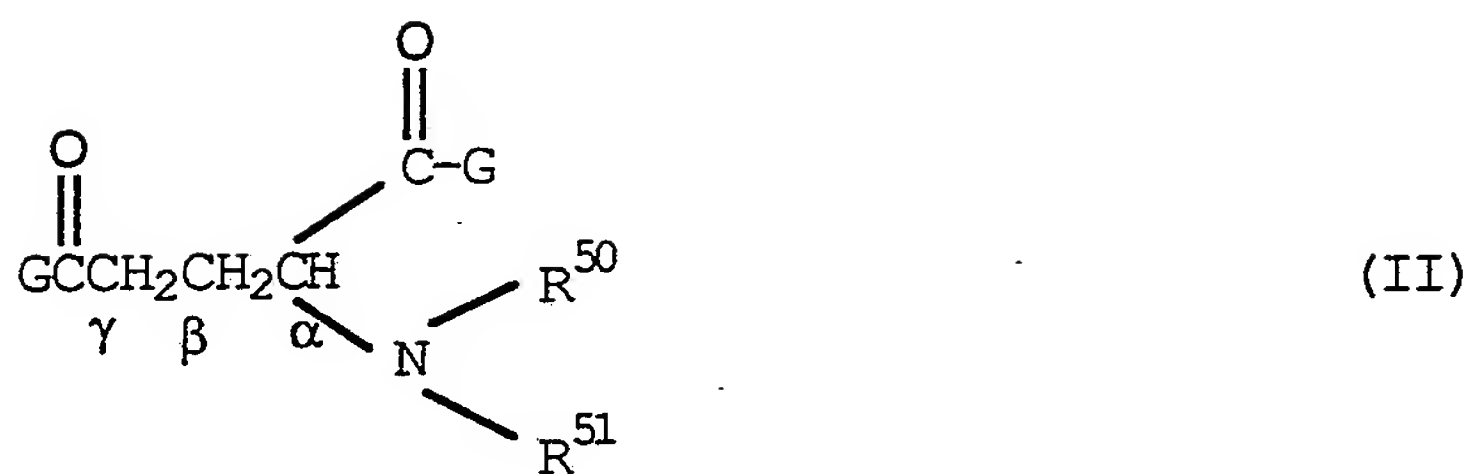
14. Conjugate of Claim 3 wherein said second  
 residue forms a kidney-enzyme-cleavable amide bond with the  
 residue of said angiotensin II antagonist compound.

30

15. Conjugate of Claim 14 wherein said second  
 residue is provided by a compound of Formula II:

**SUBSTITUTE SHEET**

306



wherein each of  $\text{R}^{50}$  and  $\text{R}^{51}$  may be independently selected from hydrido, alkylcarbonyl, alkoxy carbonyl, alkoxyalkyl, hydroxyalkyl and haloalkyl; and wherein G is selected from hydroxyl, halo, mercapto,  $-\text{OR}^{52}$ ,  $-\text{SR}^{53}$  and  $-\text{NR}^{54}$  with each of  $\text{R}^{52}$ ,  $\text{R}^{53}$  and  $\text{R}^{54}$  independently selected from hydrido and alkyl; with the proviso that said Formula II compound is selected such that formation of the cleavable amide bond occurs at carbonyl moiety attached at the gamma-position carbon of said Formula II compound.

16. Conjugate of Claim 15 wherein each G substituent is hydroxy.

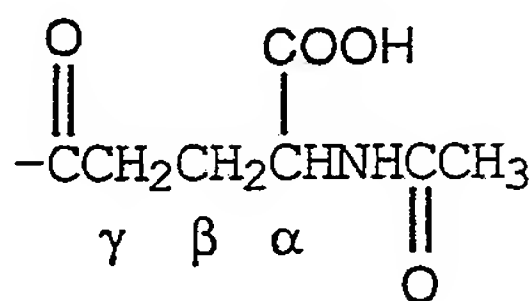
15

17. Conjugate of Claim 16 wherein each G substituent is hydroxy; wherein  $\text{R}^{50}$  is hydrido; and wherein  $\text{R}^{51}$  is selected from

20  $-\text{CR}^{55}$  wherein  $\text{R}^{55}$  is selected from methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, neopentyl, n-hexyl and chloromethyl.

18. Conjugate of Claim 17 wherein said second residue is

25



19. Conjugate of Claim 18 wherein said first residue is an angiotensin II antagonist compound containing

30

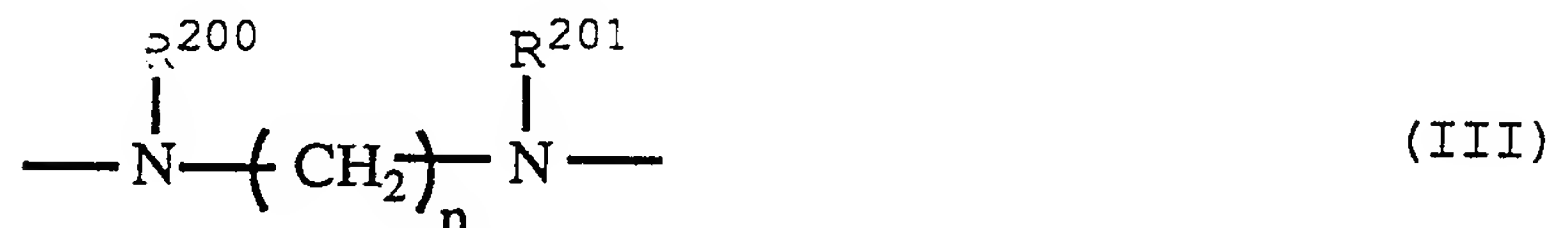
**SUBSTITUTE SHEET**

a terminal primary or secondary amino moiety selected from amino and linear or branched aminoalkyl moieties containing linear or branched alkyl groups selected from aminomethyl, aminoethyl, aminopropyl, aminoisopropyl, aminobutyl, aminosecbutyl, aminoisobutyl, aminotertbutyl, aminopentyl, aminoisopentyl and aminoneopentyl.

20. Conjugate of Claim 3 wherein said first residue is an angiotensin II antagonist compound containing a moiety convertible to a primary or secondary amino terminal moiety.

21. Conjugate of Claim 20 wherein said moiety convertible to an amino terminal moiety is a carboxylic acid group reactable with an amino moiety of a diamino-terminated linker group to provide a terminal amino moiety which may then be further reacted with a carboxylic acid moiety of a compound providing said second residue so as to form a hydrolyzable amide bond.

22. Conjugate of Claim 21 wherein said diamino-terminated linker group is a divalent radical of Formula III:

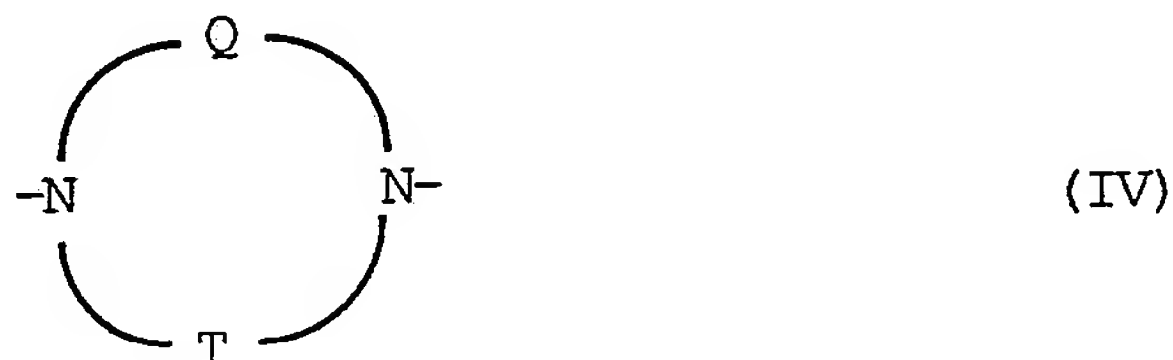


wherein each of  $\text{R}^{200}$  and  $\text{R}^{201}$  may be independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, alkoxyalkyl, hydroxyalkyl, aralkyl, aryl, haloalkyl, amino, monoalkylamino, dialkylamino, cyanoamino, carboxyalkyl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; and wherein n is zero or a number selected from three through seven, inclusive.

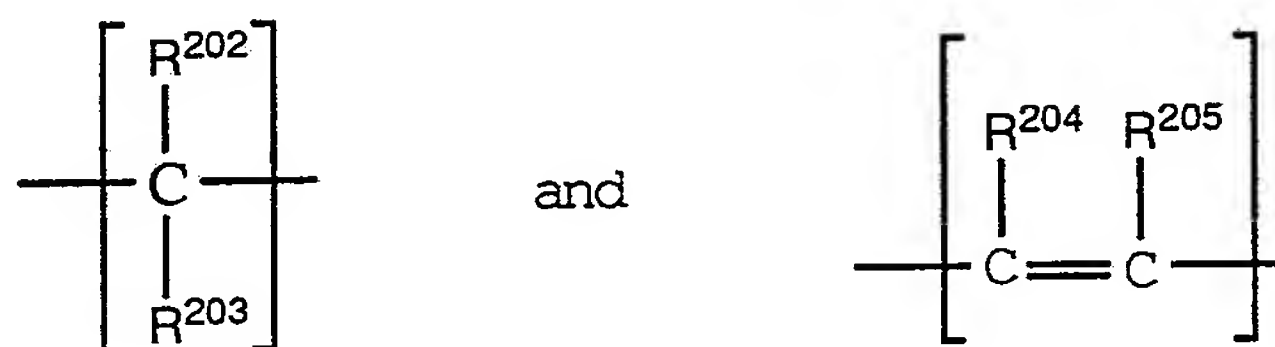


23. Conjugate of Claim 24 wherein each of  $R^{200}$  and  $R^{201}$  is hydrido.

24. Conjugate of Claim 21 wherein said diamino-terminated linker group is a divalent radical of Formula IV:



wherein each of Q and T is one or more groups independently selected from

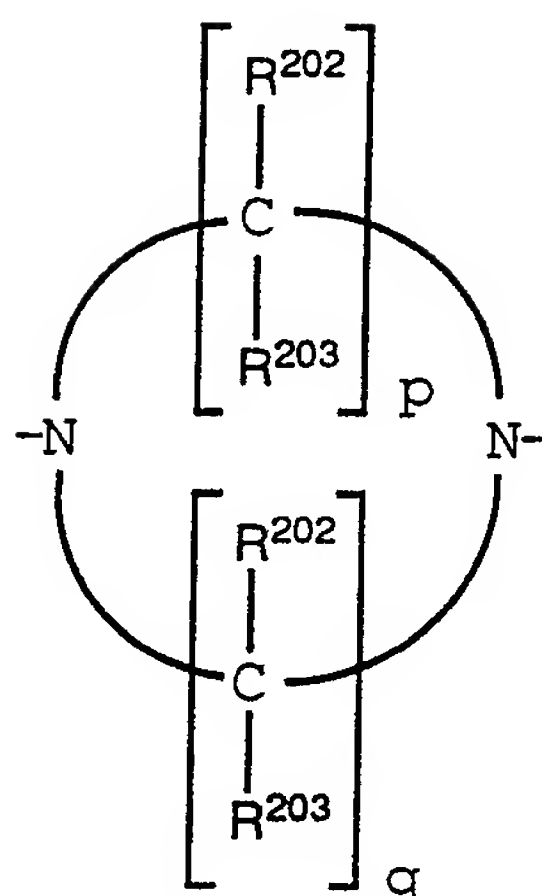


wherein each of  $R^{202}$  through  $R^{205}$  is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, aryloxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl and alkynyl.

25. Conjugate of Claim 24 wherein said diamino-terminated linker group is a divalent radical of Formula V:



309



(V)

wherein each of  $R^{202}$  and  $R^{203}$  is independently selected from hydrido, hydroxy, alkyl, phenalkyl, phenyl, alkoxy, benzyloxy, phenoxy, alkoxyalkyl, hydroxyalkyl, halo, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl and alkanoyl; and wherein each of  $p$  and  $q$  is a number independently selected from one through six, inclusive; with the proviso that when each of  $R^{202}$  and  $R^{203}$  is selected from halo, hydroxy, amino, monoalkylamino and dialkylamino, then the carbon to which  $R^{202}$  or  $R^{203}$  is attached in Formula V is not adjacent to a nitrogen atom of Formula V.

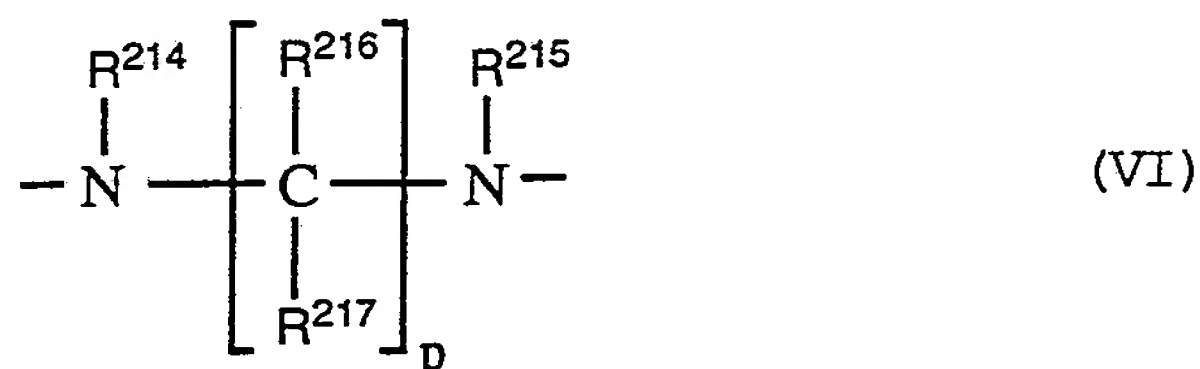
26. Conjugate of Claim 25 wherein each of  $R^{202}$  and  $R^{203}$  is independently selected from hydrido, hydroxy, alkyl, alkoxy, amino, monoalkylamino, carboxy, carboxyalkyl and alkanoyl; and wherein each of  $p$  and  $q$  is a number independently selected from two through four, inclusive.

27. Conjugate of Claim 26 wherein each of  $R^{202}$  and  $R^{203}$  is independently selected from hydrido, amino, monoalkylamino and carboxyl; and wherein each of  $p$  and  $q$  is independently selected from the numbers two and three.

28. Conjugate of Claim 27 wherein each of  $R^{202}$  and  $R^{203}$  is hydrido; and wherein each of  $p$  and  $q$  is two.

310

29. Conjugate of Claim 21 wherein said diamino-terminated linker group is a divalent radical of Formula VI:



wherein each of R<sup>214</sup> through R<sup>217</sup> is independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, hydroxyalkyl, alkoxyalkyl, aralkyl, aryl, haloalkyl, amino, monoalkylamino, dialkylamino, cyanoamino, carboxyalkyl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; and wherein p is a number selected from one through six inclusive.

30. Conjugate of Claim 29 wherein each of R<sup>214</sup> and R<sup>215</sup> is hydrido; wherein each of R<sup>216</sup> and R<sup>217</sup> is independently selected from hydrido, alkyl, phenalkyl, phenyl, alkoxyalkyl, hydroxyalkyl, haloalkyl and carboxyalkyl; and wherein p is two or three.

31. Conjugate of Claim 30 wherein each of R<sup>214</sup> and R<sup>215</sup> is hydrido; wherein each of R<sup>216</sup> and R<sup>217</sup> is independently selected from hydrido and alkyl; and wherein p is two.

32. Conjugate of Claim 31 wherein each of R<sup>214</sup>, R<sup>215</sup>, R<sup>216</sup> and R<sup>217</sup> is hydrido; and wherein p is two.

33. Conjugate of Claim 12 wherein said angiotensin II antagonist compound is 4'-[2-butyl-5-chloro-4-(hydroxymethyl)-1H-imidazol-1-ylmethyl][1,1'-biphenyl]-2-carboxylic acid.

34. Conjugate of Claim 33 which is N-acetyl-L-glutamic acid, 5-[[4'-[2-butyl-5-chloro-4-(hydroxymethyl)-

1H-imidazol-1-ylmethyl][1,1'-biphenyl]-2-yl]carbonyl]hydrazide.

35. Conjugate of Claim 33 which is N<sup>2</sup>-acetyl-N-  
5 [[2-butyl-5-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazol-4-yl]methyl]-L-glutamine.

36. Conjugate of Claim 33 which is N-acetyl-L-  
10 glutamic acid, 5-[2-butyl-5-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazol-4-yl]acetylhydrazide.

37. Conjugate of Claim 13 wherein said  
15 angiotensin II antagonist compound is 4'-[2-butyl-4-chloro-5-(hydroxymethyl)-1H-imidazol-1-ylmethyl][1,1'-biphenyl]-2-carboxylic acid.

38. Conjugate of Claim 37 which is N-acetyl-L-  
20 glutamic acid, 5-[[4'-[2-butyl-4-chloro-5-(hydroxymethyl)-1H-imidazol-1-ylmethyl][1,1'-biphenyl]-2-yl]carbonyl]hydrazide.

39. Conjugate of Claim 37 which is N<sup>2</sup>-acetyl-N-  
25 [[2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazol-5-yl]methyl]-L-glutamine.

40. Conjugate of Claim 37 which is N-acetyl-L-  
30 glutamic acid, 5-[2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazol-5-yl]acetylhydrazide.

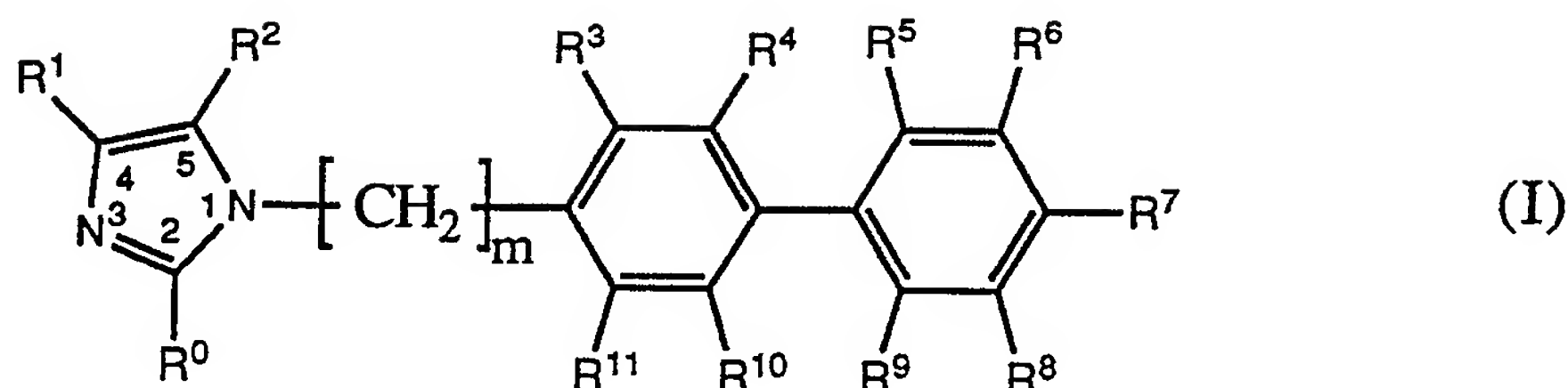
41. A pharmaceutical composition comprising one or more pharmaceutically-acceptable carriers or diluents and a therapeutically-effective amount of a renal-selective conjugate, said conjugate comprising a residue of an  
5 angiotensin II antagonist compound.

42. The composition of Claim 41 wherein said conjugate comprises first residue and a second residue, said first and second residues connected together by a  
10 cleavable bond, wherein said first residue is provided by an angiotensin II antagonist compound, and wherein said second residue is capable of being cleaved from said first residue.

43. The composition of Claim 42 wherein said first and second residues are provided by precursor compounds wherein the precursor compound of one of said first and second residues has a reactable carboxylic acid moiety and the precursor of the other of said first and  
15 second residues has a reactable amino moiety or a moiety convertible to a reactable amino moiety, whereby a cleavable bond may be formed between said carboxylic acid moiety and said amino moiety.

44. The composition of Claim 43 wherein said angiotensin II antagonist compound providing said first  
25 residue is selected from biphenylmethyl 1H-substituted-1,3-imidazole compounds.

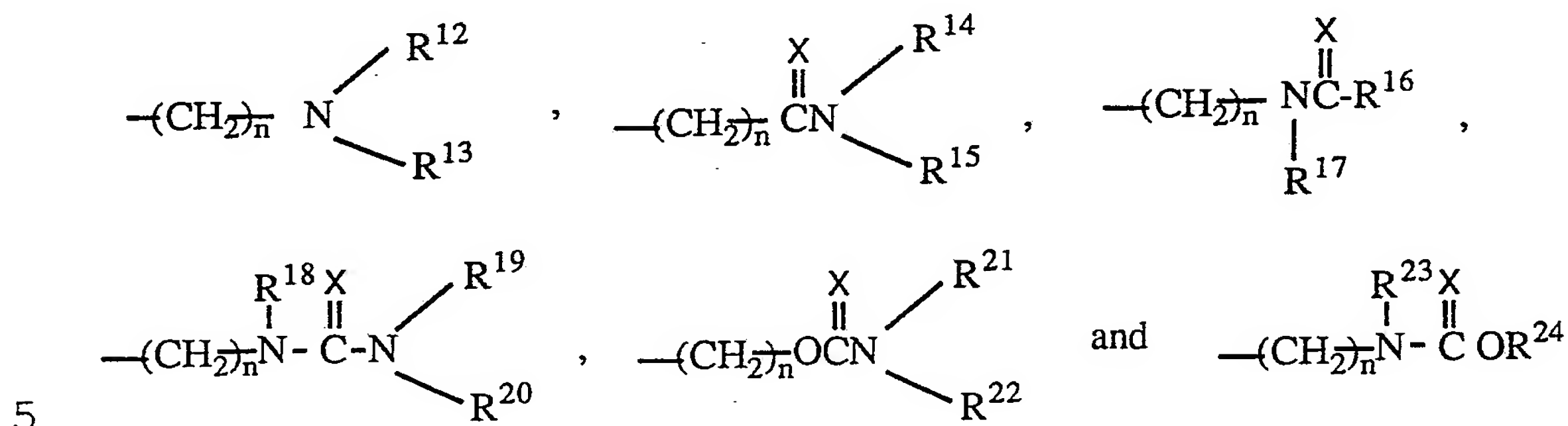
45. The composition of Claim 44 wherein said angiotensin II antagonist compound is selected from a class  
30 of compounds defined by Formula I:



wherein m is a number selected from one to four, inclusive;

- 5 wherein each of R<sup>0</sup> through R<sup>11</sup> is independently selected from hydrido, alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, formyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkylcarbonylalkyl, alkoxycarbonyl, alkenyl, 10 cycloalkenyl, alkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, mercaptocarbonyl, mercaptothiocarbonyl, mercaptoalkyl, alkoxycarbonyloxy, 15 alkylthio, cycloalkylthio, alkylthiocarbonyl, alkylcarbonylthio, alkylthiocarbonyloxy, alkylthiocarbonylthio, alkylthiothiocarbonyl, alkylthiothiocarbonylthio, arylthio, arylthiocarbonyl, arylcarbonylthio, arylthiocarbonyloxy, 20 arylthiocarbonylthio, arylthiothiocarbonyl, arylthiothiocarbonylthio, aralkylthio, aralkylthiocarbonyl, aralkylcarbonylthio, aralkylthiocarbonyloxy, aralkylthiocarbonylthio, alkylthiocarbonyl, aralkylthiocarbonylthio, mercapto, alkylsulfinyl, 25 alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, phthalimido, phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and cycloheteroalkylcarbonylalkyl wherein each of said heteroaryl- and cyclohetero-containing 30 groups has one or more ring atoms selected from oxygen,

sulfur and nitrogen atoms, and wherein each of  $R^0$  through  $R^{11}$  may be further independently selected from amino and amido radicals of the formula



wherein X is oxygen atom or sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

wherein each of  $R^{12}$  through  $R^{24}$  is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl, and wherein  $R^{12}$  and  $R^{13}$  taken together,  $R^{14}$  and  $R^{15}$  taken together,  $R^{16}$  and  $R^{17}$  taken together,  $R^{19}$  and  $R^{20}$  taken together and  $R^{21}$  and  $R^{22}$  taken together may each form a heterocyclic group having five to seven ring members including the nitrogen atom of said amino or amido radical and which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms and which heterocyclic group may be saturated or partially unsaturated; wherein  $R^{12}$  and  $R^{13}$  taken together,  $R^{14}$  and  $R^{15}$  taken together,  $R^{19}$  and  $R^{20}$  taken together and  $R^{21}$  and  $R^{22}$  taken together may each form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino or amido radical and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms;

**SUBSTITUTE SHEET**

and wherein each of  $R^3$  through  $R^{11}$  may be further independently selected from hydrido and haloalkyl, and from acidic moieties of the formula

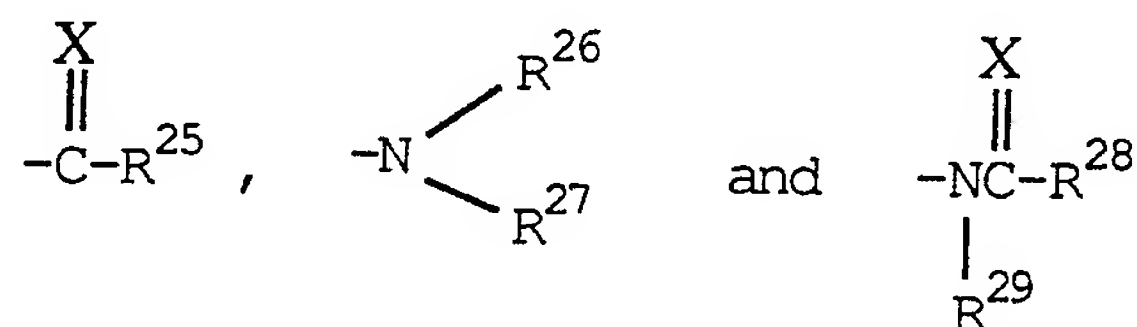
5



wherein  $n$  is a number selected from zero through three, inclusive, and wherein  $A$  is an acidic group selected to contain at least one acidic hydrogen atom, and the amide, ester and salt derivatives of said acidic moieties; wherein  $Y$  is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aryl, aralkyl and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms;

and wherein any of the foregoing  $R^1$  through  $R^{24}$ ,  $Y$  and  $A$  groups having a substitutable position may be substituted with one or more groups selected from hydroxy, alkyl, alkenyl, alkynyl, aralkyl, hydroxyalkyl, trifluoromethyl, difluoroalkyl, oxo, alkoxy, aryloxy, aralkoxy, aralkylthio, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, aroyl, cycloalkenyl, cyano, cyanoamino, nitro, alkylcarbonyloxy, alkoxy carbonyloxy, alkylcarbonyl, alkoxy carbonyl, carboxyl, mercapto, mercaptocarbonyl, alkylthio, arylthio, alkylthiocarbonyl, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms, and amino and amido radicals of the formula

30

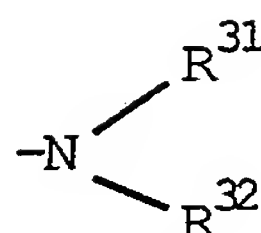


wherein  $X$  is selected from oxygen atom and sulfur atom; wherein  $R^{25}$  is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl,  $DR^{30}$  and

35

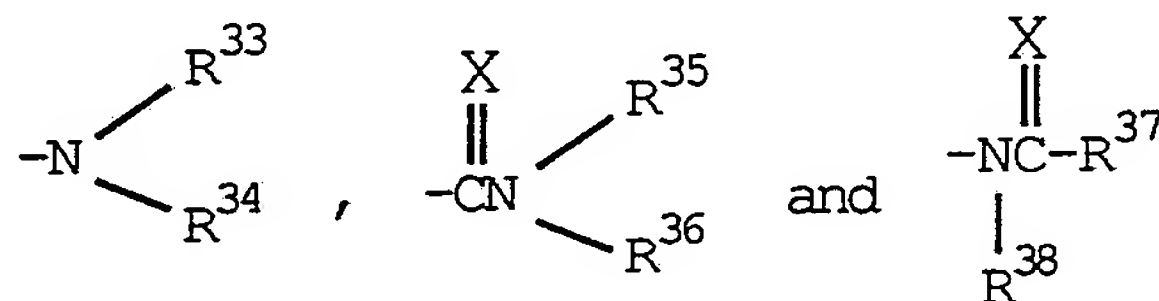


316



wherein D is selected from oxygen atom and sulfur atom and  
 5 R<sup>30</sup> is selected from hydrido, alkyl, cycloalkyl,  
 cycloalkylalkyl, aralkyl and aryl; wherein each of R<sup>25</sup>,  
 R<sup>26</sup>, R<sup>27</sup>, R<sup>28</sup>, R<sup>29</sup>, R<sup>31</sup> and R<sup>32</sup> is independently selected  
 from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl,  
 haloalkyl, cycloalkylalkyl, alkoxyalkyl, alkylcarbonyl,  
 10 alkoxy carbonyl, carboxyl, alkylsulfinyl, alkylsulfonyl,  
 arylsulfinyl, arylsulfonyl, haloalkylsulfinyl,  
 haloalkylsulfonyl, aralkyl and aryl, and wherein each of  
 R<sup>26</sup>, R<sup>27</sup>, R<sup>28</sup>, R<sup>29</sup>, R<sup>31</sup> and R<sup>32</sup> is further independently  
 selected from amino and amido radicals of the formula

15



wherein X is oxygen atom or sulfur atom;

20 wherein each of R<sup>33</sup>, R<sup>34</sup>, R<sup>35</sup>, R<sup>36</sup>, R<sup>37</sup> and R<sup>38</sup> is  
 independently selected from hydrido, alkyl, cycloalkyl,  
 cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl,  
 cycloalkylalkyl, alkoxyalkyl, haloalkylsulfinyl,  
 haloalkylsulfonyl, aralkyl and aryl, and wherein R<sup>26</sup> and  
 25 R<sup>27</sup> taken together and R<sup>28</sup> and R<sup>29</sup> taken together may each  
 form a heterocyclic group having five to seven ring members  
 including the nitrogen atom of said amino or amido radical,  
 which heterocyclic group may further contain one or more  
 hetero atoms as ring members selected from oxygen, nitrogen  
 30 and sulfur atoms and which heterocyclic group may be  
 saturated or partially unsaturated; wherein R<sup>26</sup> and R<sup>27</sup>  
 taken together and R<sup>31</sup> and R<sup>32</sup> taken together may each form  
 an aromatic heterocyclic group having five ring members  
 including the nitrogen atom of said amino or amido radical



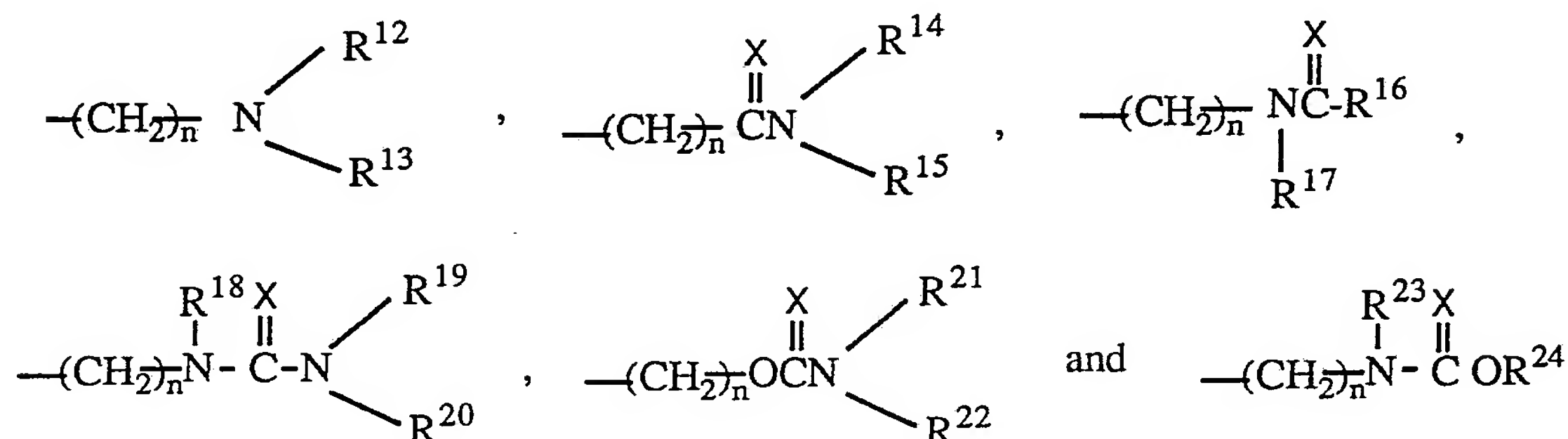
and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms;

- 5 with the proviso that at least one of said  $R^1$  through  $R^{24}$ , Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;
- 10 or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

46. The composition of Claim 45 wherein m is one; wherein each of  $R^0$  through  $R^{11}$  is independently  
15 selected from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, cyano, nitro, carboxyl,  
20 carboxyalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, mercaptocarbonyl, mercaptothiocarbonyl, mercaptoalkyl, alkoxycarbonyloxy, alkylthio, cycloalkylthio, alkylthiocarbonyl,  
25 alkylcarbonylthio, alkylthiocarbonyloxy, alkylthio-carbonylthio, alkylthiothiocarbonyl, alkylthiothio-carbonylthio, arylthio, arylthiocarbonyl, arylcarbonylthio, arylthiocarbonyloxy, arylthiocarbonylthio, arylthiothiocarbonyl, arylthiothiocarbonylthio,  
30 aralkylthio, aralkylthiocarbonyl, aralkylcarbonylthio, aralkylthiocarbonyloxy, aralkylthiocarbonylthio, aralkylthiocarbonyl, aralkylthiocarbonylthio, mercapto, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, phthalimido,  
35 phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and cycloheteroalkylcarbonylalkyl wherein each of said heteroaryl- and cycloheteroalkyl-containing groups has

one or more hetero ring atoms selected from oxygen, sulfur and nitrogen atoms, and wherein each of  $R^0$  through  $R^{11}$  may be further independently selected from amino and amido radicals of the formula

5



wherein X is selected from oxygen atom or sulfur atom;

10

wherein each n is a number independently selected from zero to six, inclusive;

wherein each of  $R^{12}$  through  $R^{24}$  is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl;

15

and wherein each of  $R^3$  through  $R^{11}$  may be further independently selected from hydrido and haloalkyl, and from acidic moieties of the formula

20

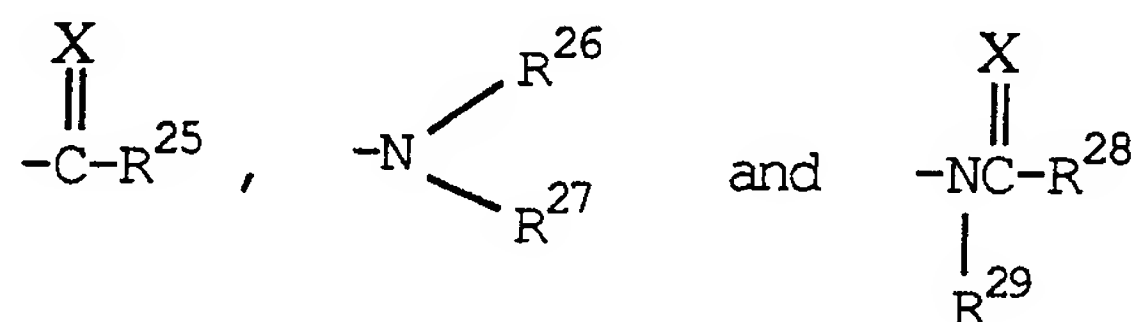


wherein n is a number selected from zero through three, inclusive; wherein A is an acidic group selected from acids containing one or more atoms selected from oxygen, sulfur, phosphorus and nitrogen atoms, and wherein said acidic group is selected to contain at least one acidic hydrogen atom, and the amide, ester and salt derivatives of said acidic moieties; wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl,

30

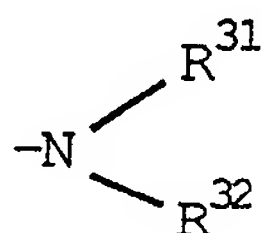
cycloalkylalkyl, alkenyl, alkynyl, aryl, aralkyl and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms;

- 5 and wherein any of the foregoing  $R^1$  through  $R^{24}$ , Y and A groups having a substitutable position may be substituted with one or more groups selected from alkyl, alkenyl, aralkyl, hydroxyalkyl, trifluoromethyl, difluoroalkyl, alkoxy, aryloxy, aralkoxy, alkoxyalkyl, alkylcarbonyl, 10 alkoxy carbonyl, carboxyl, mercaptocarbonyl, alkylthio, alkylthiocarbonyl, and amino and amido radicals of the formula



15

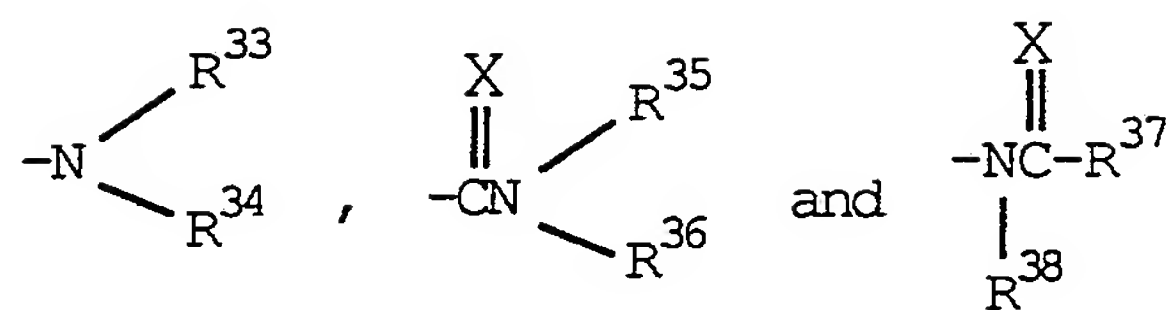
wherein X is selected from oxygen atom and sulfur atom; wherein  $R^{25}$  is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, and  $\text{DR}^{30}$  and



20

- wherein D is selected from oxygen atom and sulfur atom, and  $R^{30}$  is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl and aryl; wherein each of  $R^{26}$ , 25  $R^{27}$ ,  $R^{28}$ ,  $R^{29}$ ,  $R^{31}$  and  $R^{32}$  is independently selected from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, alkanoyl, alkoxy carbonyl, carboxyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl, and wherein each of  $R^{26}$ ,  $R^{27}$ ,  $R^{28}$ ,  $R^{29}$ ,  $R^{31}$  and  $R^{32}$  30 is further independently selected from amino and amido radicals of the formula

320



wherein X is selected from oxygen atom or sulfur atom;

- 5 wherein each of R<sup>26</sup> through R<sup>31</sup> is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl;

10

with the proviso that at least one of said R<sup>1</sup> through R<sup>24</sup>, Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

15

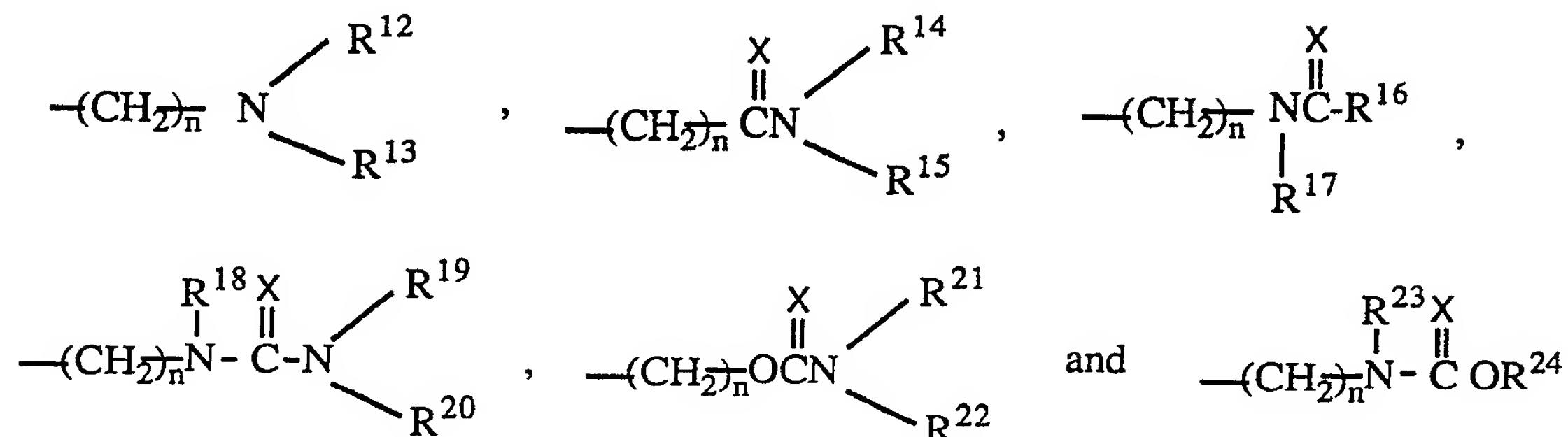
or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

47. The composition of Claim 46 wherein m is  
 20 one; wherein each of R<sup>0</sup> through R<sup>11</sup> is independently selected from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cycloalkenyl,  
 25 alkynyl, cycloalkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, mercaptocarbonyl, alkoxycarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, alkylthio, cycloalkylthio,  
 30 arylthio, aralkylthio, aralkylthiocarbonylthio, mercapto, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, phthalimido, phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and  
 35 cycloheteroalkylcarbonylalkyl wherein each of said heteroaryl- and cycloheteroalkyl-containing groups has one

321

or more hetero ring atoms selected from oxygen, sulfur and nitrogen atoms, and wherein each of  $R^0$  through  $R^{11}$  may be further independently selected from amino and amido radicals of the formula

5



10

wherein X is selected from oxygen atom or sulfur atom;

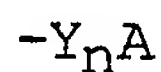
wherein each n is a number independently selected from zero to six, inclusive;

15

wherein each of  $R^{12}$  through  $R^{24}$  is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl;

20

and wherein each of  $R^3$  through  $R^{11}$  may be an acidic moiety further independently selected from hydrido and haloalkyl, and from acidic moieties of the formula



25

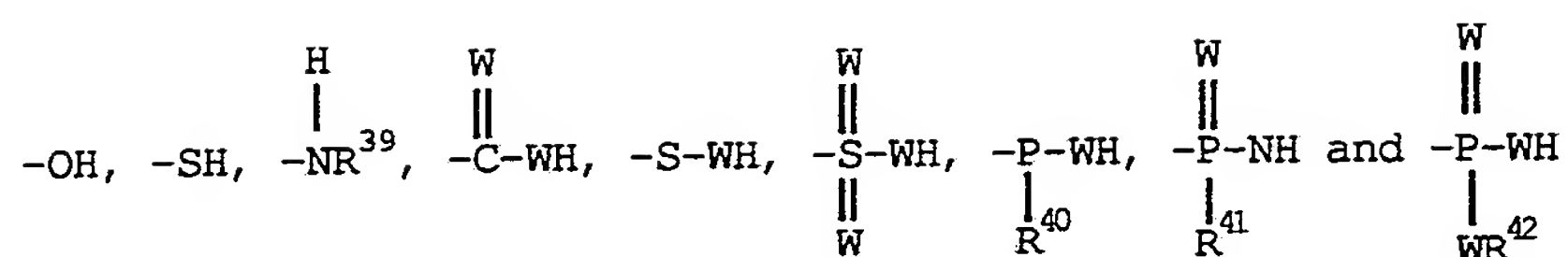
wherein n is a number selected from zero through three, inclusive;

wherein A is selected from carboxylic acid and bioisosteres of carboxylic acid selected from

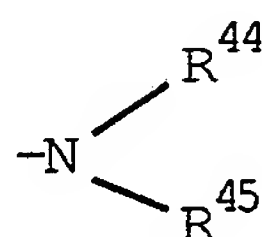
30

**SUBSTITUTE SHEET**

322



wherein each W is independently selected from oxygen atom, sulfur atom and  $\text{NR}^{43}$ ; wherein each of  $\text{R}^{39}$ ,  $\text{R}^{40}$ ,  $\text{R}^{41}$ ,  $\text{R}^{42}$  and  $\text{R}^{43}$  is independently selected from hydrido, alkyl, haloalkyl, haloalkylsulfonyl, haloalkylcarbonyl, cycloalkyl, cycloalkylalkyl, aryl and aralkyl; wherein each of  $\text{R}^{39}$ ,  $\text{R}^{40}$ ,  $\text{R}^{41}$  and  $\text{R}^{42}$  may be further independently selected from amino radicals of the formula



wherein each of  $\text{R}^{44}$  and  $\text{R}^{45}$  is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl, and wherein  $\text{R}^{44}$  and  $\text{R}^{45}$  taken together may form a heterocyclic group having five to seven ring members including the nitrogen atom of said amino radical, which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms and which heterocyclic group may be saturated or partially unsaturated; wherein  $\text{R}^{44}$  and  $\text{R}^{45}$  taken together may form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino radical and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms; wherein each of  $\text{R}^{40}$  and  $\text{R}^{41}$  may be further independently selected from hydroxy, alkoxy, alkylthio, aryloxy, arylthio, aralkylthio and aralkoxy; and the amide, ester and salt derivatives of said acidic groups;

wherein said bioisostere of carboxylic acid may be further selected from heterocyclic acidic groups consisting of

**SUBSTITUTE SHEET**

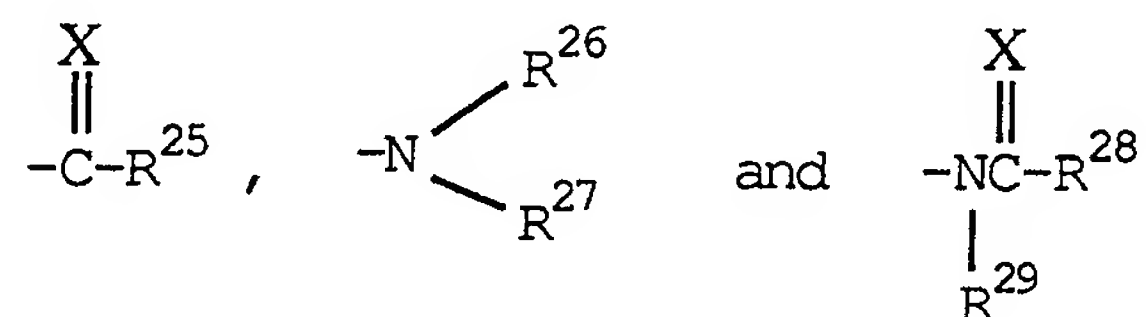


heterocyclic rings of four to about nine ring members,  
 which heterocyclic ring contains at least one hetero atom  
 selected from oxygen, sulfur and nitrogen atoms, which  
 heterocyclic ring may be saturated, fully unsaturated or  
 5 partially unsaturated, and which heterocyclic ring may be  
 attached at a single position selected from R<sup>3</sup> through R<sup>11</sup>  
 or may be attached at any two adjacent positions selected  
 from R<sup>3</sup> through R<sup>11</sup> so as to form a fused-ring system with  
 one of the phenyl rings of the biphenyl moiety of Formula  
 10 I; and the amide, ester and salt derivatives of said  
 heterocyclic acidic groups;

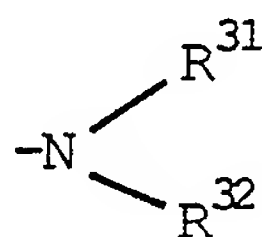
wherein Y is a spacer group independently selected from one  
 or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl,  
 15 aryl and aralkyl;

and wherein any of the foregoing R<sup>1</sup> through R<sup>24</sup>, Y and A  
 groups having a substitutable position may be substituted  
 by one or more groups selected from alkyl, difluoroalkyl,  
 20 alkenyl, aralkyl, hydroxyalkyl, trifluoromethyl, alkoxy,  
 aryloxy, aralkoxy, alkoxyalkyl, alkylcarbonyl,  
 alkoxycarbonyl, carboxyl, mercaptocarbonyl, alkylthio,  
 alkylthiocarbonyl, and amino and amido radicals of the  
 formula

25



wherein X is selected from oxygen atom and sulfur atom;  
 wherein R<sup>25</sup> is selected from hydrido, alkyl, cycloalkyl,  
 30 cycloalkylalkyl, aralkyl, aryl and DR<sup>30</sup> and



**SUBSTITUTE SHEET**

wherein D is selected from oxygen atom and sulfur atom,  
wherein R<sup>30</sup> is selected from hydrido, alkyl, cycloalkyl,  
cycloalkylalkyl, aralkyl and aryl;

5 wherein each of R<sup>26</sup>, R<sup>27</sup>, R<sup>28</sup>, R<sup>29</sup>, R<sup>31</sup> and R<sup>32</sup> is  
independently selected from hydrido, alkyl, cycloalkyl,  
cyano, hydroxyalkyl, haloalkyl, cycloalkylalkyl,  
alkoxyalkyl, alkanoyl, alkoxycarbonyl, carboxyl,  
haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl;

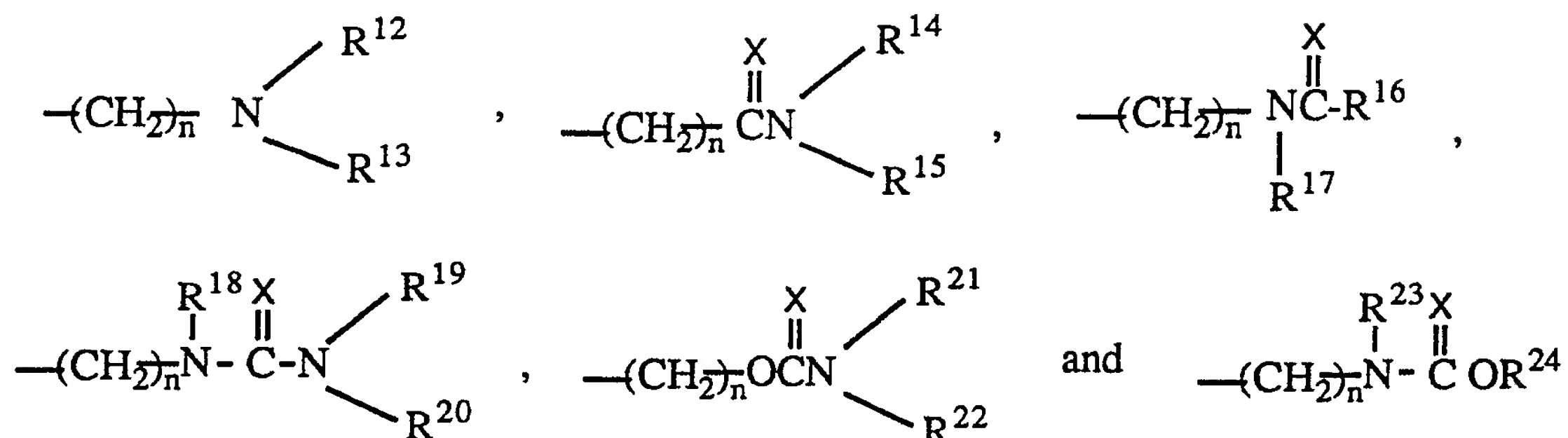
10 with the proviso that at least one of said R<sup>1</sup> through R<sup>24</sup>,  
Y and A substituents contains a terminal primary or  
secondary amino moiety or a moiety convertible to a primary  
or secondary amino moiety;

15 or a tautomer thereof or a pharmaceutically-acceptable salt  
thereof.

48. The composition of Claim 47 wherein m is  
20 one; wherein each of R<sup>0</sup>, R<sup>1</sup> and R<sup>2</sup> is independently  
selected from alkyl, hydroxyalkyl, halo, haloalkyl,  
cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl,  
aryloxy, aryloxyalkyl, aralkoxy, alkoxyalkyl,  
alkylcarbonyl, alkoxycarbonyl, alkenyl, cycloalkenyl,  
25 alkynyl, cycloalkynyl, cyano, nitro, carboxyl,  
carboxyalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl,  
alkoxycarbonylalkyl, aralkoxycarbonylalkyl,  
aralkylcarbonyloxyalkyl, mercaptoalkyl, mercaptoalkyl,  
alkoxycarbonyloxy, alkylthio, cycloalkylthio, arylthio,  
30 aralkylthio, mercapto, alkylsulfinyl, alkylsulfonyl,  
aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl,  
arylsulfonyl, phthalimido, phthalimidoalkyl, heteroaryl,  
heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl  
and cycloheteroalkylcarbonylalkyl wherein each of said  
35 heteroaryl- and cycloheteroalkyl-containing groups has one  
or more hetero ring atoms selected from oxygen, sulfur and  
nitrogen atoms, and wherein each of R<sup>0</sup> through R<sup>11</sup> may be



further independently selected from amino and amido radicals of the formula



wherein X is selected from oxygen atom and sulfur atom;

wherein each n is a number independently selected from zero  
10 to six, inclusive;

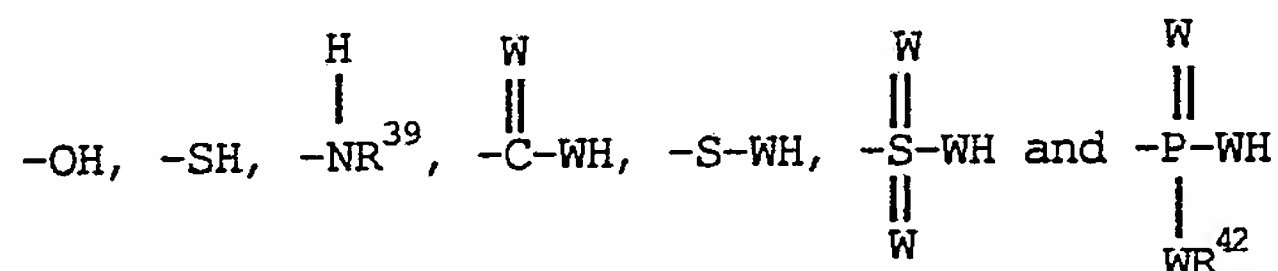
wherein each of R<sup>12</sup> through R<sup>24</sup> is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl;

wherein each of R<sup>3</sup> through R<sup>11</sup> is independently selected from hydrido, hydroxy, alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxy carbonyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, cyano, nitro, carboxyl, alkylthio, aralkylthio, mercapto, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms;

and wherein each of R<sup>3</sup> through R<sup>11</sup> may be an acidic moiety further independently selected from acidic moieties of the formula



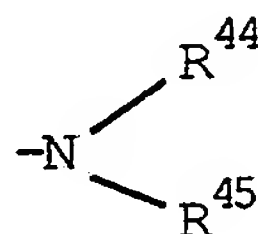
wherein n is a number selected from zero through three, inclusive; wherein A is selected from carboxylic acid and bioisosteres of carboxylic acid selected from



5

wherein each W is independently selected from oxygen atom, sulfur atom and  $\text{NR}^{43}$ ; wherein each of  $\text{R}^{39}$ ,  $\text{R}^{42}$  and  $\text{R}^{43}$  is independently selected from hydrido, alkyl, haloalkyl, haloalkylsulfonyl, haloalkylcarbonyl, cycloalkyl, cycloalkylalkyl, aryl and aralkyl; wherein each of  $\text{R}^{39}$  and  $\text{R}^{42}$  may be further independently selected from amino radical of the formula

15



wherein each of  $\text{R}^{44}$  and  $\text{R}^{45}$  is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl, and wherein  $\text{R}^{44}$  and  $\text{R}^{45}$  taken together may form a heterocyclic group having five to seven ring members including the nitrogen atom of said amino radical, which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms, and which heterocyclic group may be saturated or partially unsaturated; wherein  $\text{R}^{44}$  and  $\text{R}^{45}$  taken together may form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino radical and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms; and the amide, ester and salt derivatives of said acidic groups; wherein said bioisostere of carboxylic acid may be further selected from heterocyclic acidic groups consisting of heterocyclic rings of four to about nine ring members, which ring contains at least one

35

hetero atom, selected from oxygen, sulfur and nitrogen atoms, which heterocyclic ring may be saturated, fully unsaturated or partially unsaturated, and which

heterocyclic ring may be attached at a single position  
5 selected from  $R^3$  through  $R^{11}$  or may be attached at any two adjacent positions selected from  $R^3$  through  $R^{11}$  so as to form a fused-ring system with one of the phenyl rings of Formula I; and the amide, ester and salt derivatives of said heterocyclic acidic groups;

10

wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, aryl and aralkyl;

15 wherein each of  $R^1$  through  $R^{24}$ , Y and A independently may be substituted at any substitutable position with one or more groups selected from alkyl, cycloalkyl, cycloalkylalkyl, hydroxy, oxo, trifluoromethyl, difluoroalkyl, alkoxycarbonyl, cyano, nitro, alkylsulfonyl,  
20 haloalkylsulfonyl, aryl, aralkyl, alkoxy, aryloxy and aralkoxy;

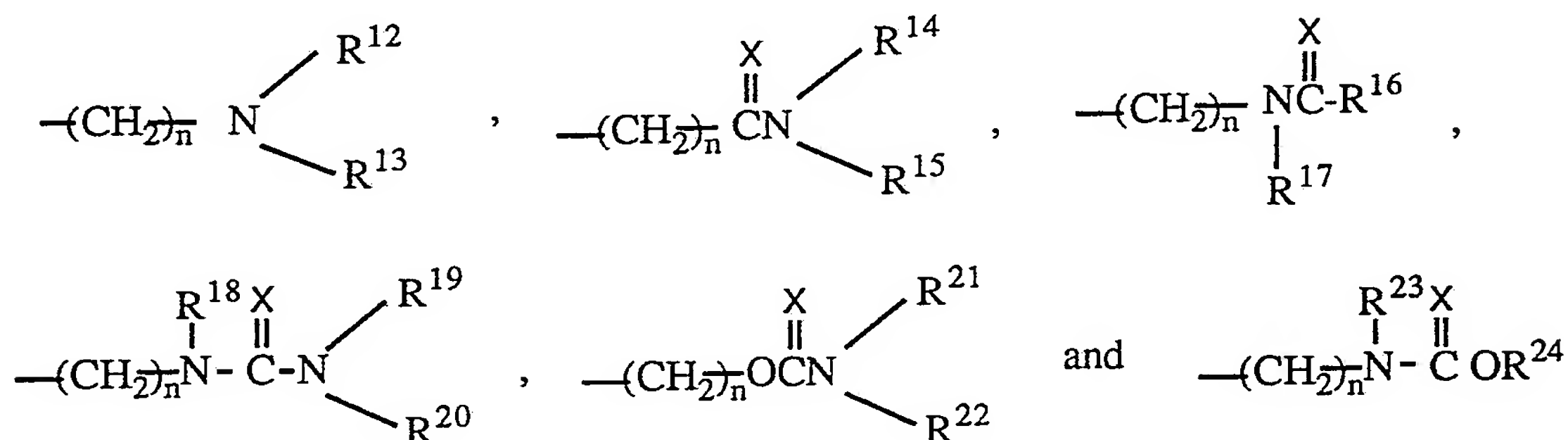
with the proviso that at least one of said  $R^1$  through  $R^{24}$ , Y and A substituents contains a terminal primary or  
25 secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

30

49. The composition of Claim 48 wherein m is one; wherein each of  $R^0$ ,  $R^1$  and  $R^2$  is independently selected from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl,  
35 benzoyl, phenoxy, phenoxyalkyl, phenalkyloxy, phenylthio, phenalkylthio, aralkoxy, alkoxycarbonyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy,

alkylcarbonyloxyalkyl, alkoxycarbonylalkyl,  
 aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl,  
 mercaptocarbonyl, mercaptoalkyl, alkoxycarbonyloxy,  
 alkylthio, cycloalkylthio, phthalimido, phthalimidoalkyl,  
 5 heteroaryl, heteroarylalkyl, cycloheteroalkyl,  
 cycloheteroalkylalkyl and cycloheteroalkylcarbonylalkyl  
 wherein each of said heteroaryl- and cycloheteroalkyl-  
 containing groups has one or more hetero ring atoms  
 selected from oxygen, sulfur and nitrogen atoms, and  
 10 wherein each of  $R^0$  through  $R^{11}$  may be further independently  
 selected from amino and amido radicals of the formula



15

wherein X is selected from oxygen atom and sulfur atom;

wherein each n is a number independently selected from zero  
 to six, inclusive;

20

wherein each of  $R^{12}$  through  $R^{24}$  is independently selected  
 from hydrido, alkyl, cycloalkyl, cyano, amino,  
 hydroxyalkyl, alkoxyalkyl, phenalkyl and phenyl;

25

wherein each of  $R^3$  through  $R^{11}$  is independently selected  
 from hydrido, hydroxy, alkyl, hydroxyalkyl, halo,  
 haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, phenalkyl,  
 phenyl, benzoyl, phenoxy, phenalkyloxy, alkoxyalkyl,  
 alkylcarbonyl, alkoxycarbonyl, alkenyl, cyano, nitro,  
 30 carboxyl, alkylthio, mercapto and heteroaryl having one or  
 more ring atoms selected from oxygen, sulfur and nitrogen  
 atoms;

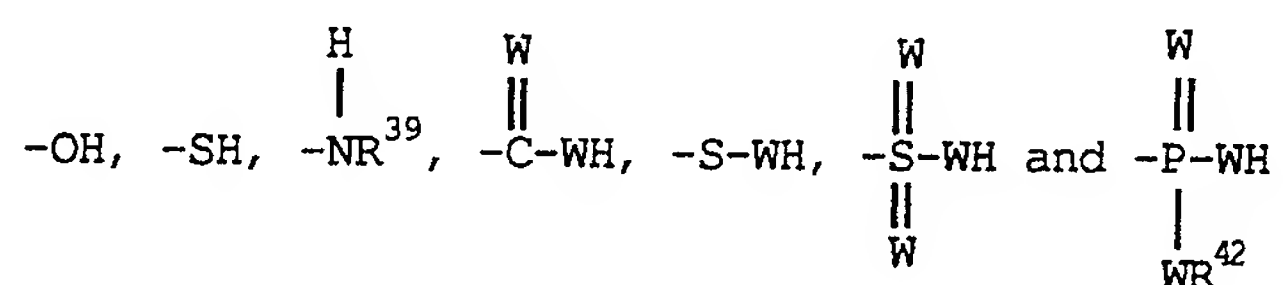
and wherein each of R<sup>3</sup> through R<sup>11</sup> may be an acidic moiety further independently selected from acidic moieties of the formula

5



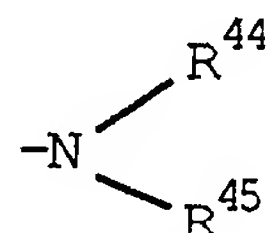
wherein n is a number selected from zero through two, inclusive; wherein A is selected from carboxylic acid and bioisosteres of carboxylic acid selected from

10



wherein each W is independently selected from oxygen atom, sulfur atom and NR<sup>43</sup>; wherein each of R<sup>39</sup>, R<sup>42</sup> and R<sup>43</sup> is independently selected from hydrido, alkyl, haloalkyl, haloalkylsulfonyl, haloalkylcarbonyl, cycloalkyl, phenyl and benzyl; wherein each of R<sup>39</sup> and R<sup>42</sup> may be further independently selected from amino radical of the formula

15



20

wherein each of R<sup>44</sup> and R<sup>45</sup> is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, alkoxyalkyl, benzyl and phenyl; and the amide, ester and salt derivatives of said acidic groups;

25

wherein said bioisostere of carboxylic acid may be further selected from heterocyclic acidic groups consisting of heterocyclic rings of four to about nine ring members, which ring contains at least one hetero atom, selected from oxygen, sulfur and nitrogen atoms, which heterocyclic ring may be saturated, fully unsaturated or partially unsaturated, and which heterocyclic ring may be attached at a single position selected from R<sup>3</sup> through R<sup>11</sup> or may be attached at any two adjacent positions selected from R<sup>3</sup>

30

35

through R<sup>11</sup> so as to form a fused-ring system with one of the phenyl rings of the biphenyl moiety of Formula I; and the amide, ester and salt derivatives of said heterocyclic acidic groups;

5

wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, phenyl, phenalkyl and aralkyl;

10

wherein each of R<sup>1</sup> through R<sup>24</sup>, Y and A and independently may be substituted at any substitutable position with one or more groups selected from alkyl, cycloalkyl, cycloalkylalkyl, hydroxy, oxo, trifluoromethyl, difluoroalkyl, alkoxycarbonyl, cyano, nitro, alkylsulfonyl, haloalkylsulfonyl, aryl, aralkyl, alkoxy, aryloxy and aralkoxy;

15

with the proviso that at least one of said R<sup>1</sup> through R<sup>24</sup>, Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

20

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

25

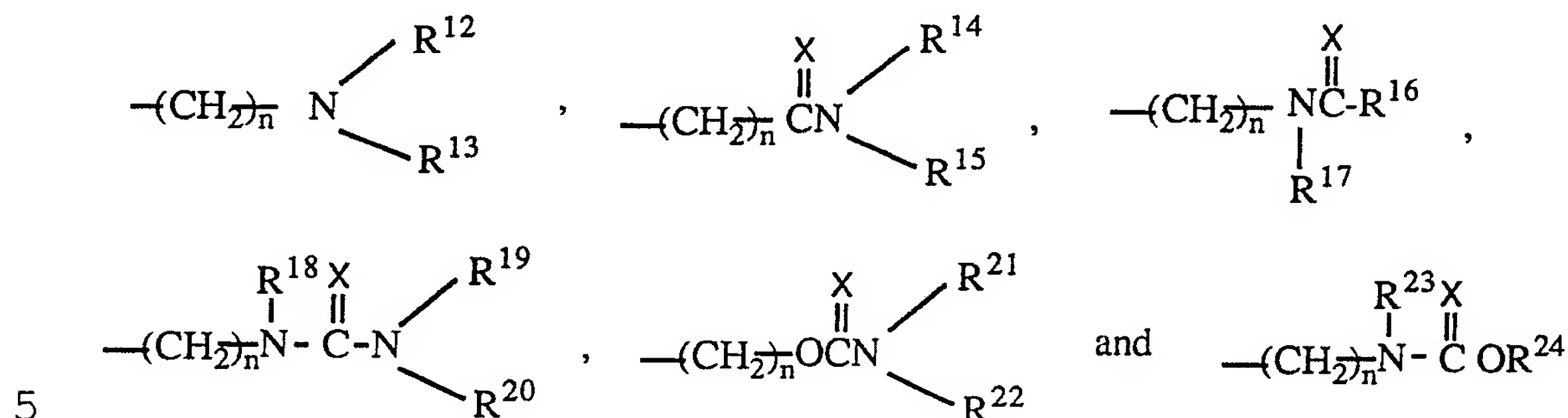
50. The composition of Claim 49 wherein m is one; wherein R<sup>0</sup> is selected from alkyl, alkenyl, phenyl, alkylthio, cycloalkyl, cycloalkylalkyl and cycloalkylthio; wherein each of R<sup>1</sup> and R<sup>2</sup> is independently selected from alkyl, aminoalkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, benzoyl, phenoxy, phenoxyalkyl, phenalkyloxy, phenylthio, phenalkylthio, aralkoxy, alkoxyalkyl, acetyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, mercaptoalkyl, mercaptocarbonyl, alkoxycarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl,

30

35



phthalimido, phthalimidoalkyl, imidazoalkyl, tetrazole, tetrazolealkyl, alkylthio, cycloalkylthio, and amino and amido radicals of the formula



wherein X is selected from oxygen atom and sulfur atom;

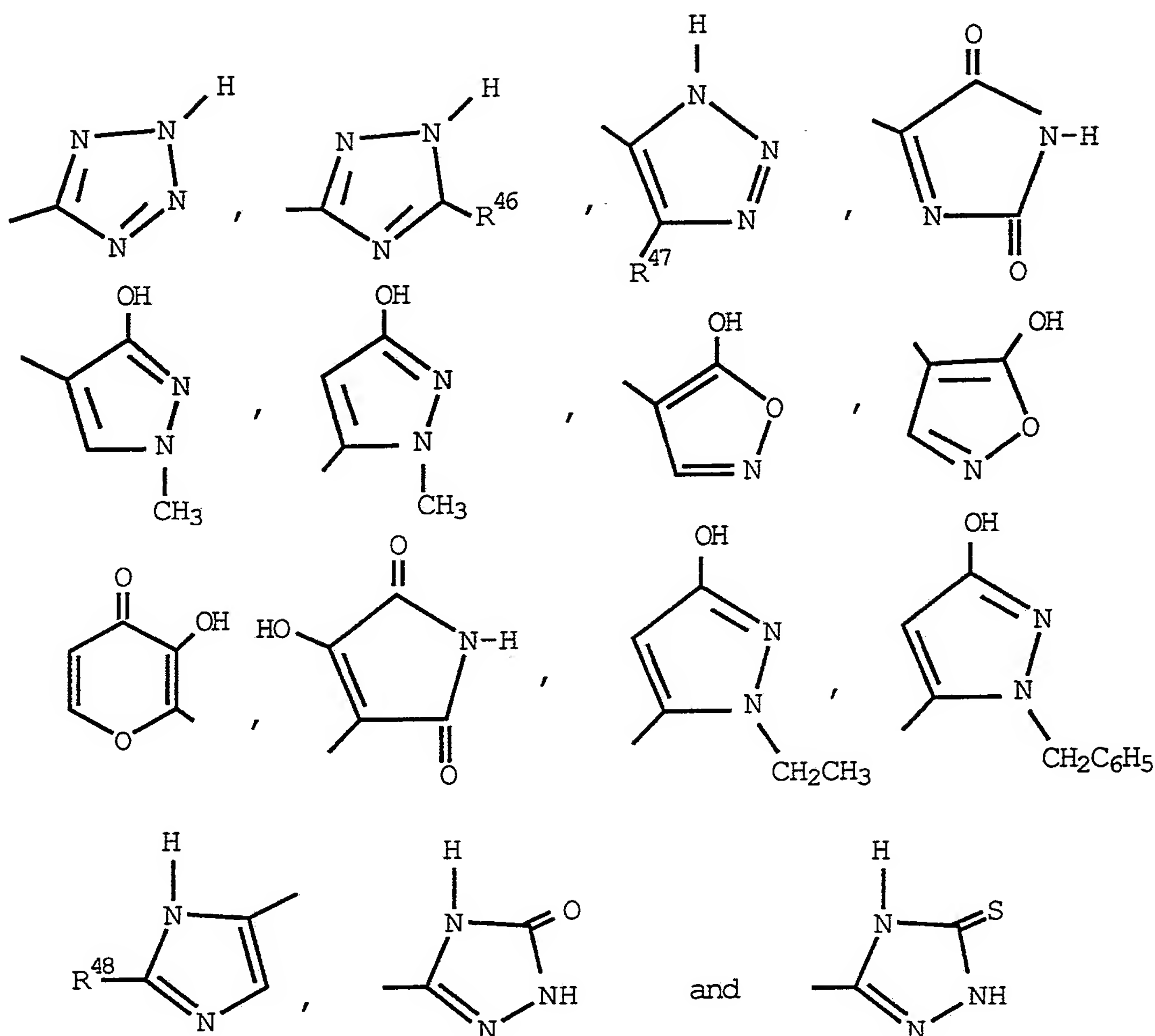
wherein each n is a number independently selected from zero to six, inclusive;

wherein each of R<sup>12</sup> through R<sup>24</sup> is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, hydroxyalkyl, alkoxyalkyl, phenalkyl and phenyl;

wherein each of R<sup>3</sup> through R<sup>11</sup> is independently selected from hydrido, hydroxy, alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, phenalkyl, phenyl, benzoyl, phenoxy, phenalkyloxy, alkoxyalkyl, acetyl, alkoxycarbonyl, alkenyl, cyano, nitro, carboxyl, alkylthio and mercapto;

and wherein each of R<sup>3</sup> through R<sup>11</sup> may be an acidic moiety further independently selected from acidic moieties consisting of CO<sub>2</sub>H, CO<sub>2</sub>CH<sub>3</sub>, SH, CH<sub>2</sub>SH, C<sub>2</sub>H<sub>4</sub>SH, PO<sub>3</sub>H<sub>2</sub>, NHSO<sub>2</sub>CF<sub>3</sub>, NHSO<sub>2</sub>C<sub>6</sub>F<sub>5</sub>, SO<sub>3</sub>H, CONHNH<sub>2</sub>, CONHNHSO<sub>2</sub>CF<sub>3</sub>, CONHOCH<sub>3</sub>, CONHOC<sub>2</sub>H<sub>5</sub>, CONHCF<sub>3</sub>, OH, CH<sub>2</sub>OH, C<sub>2</sub>H<sub>4</sub>OH, OPO<sub>3</sub>H<sub>2</sub>, OSO<sub>3</sub>H,

332

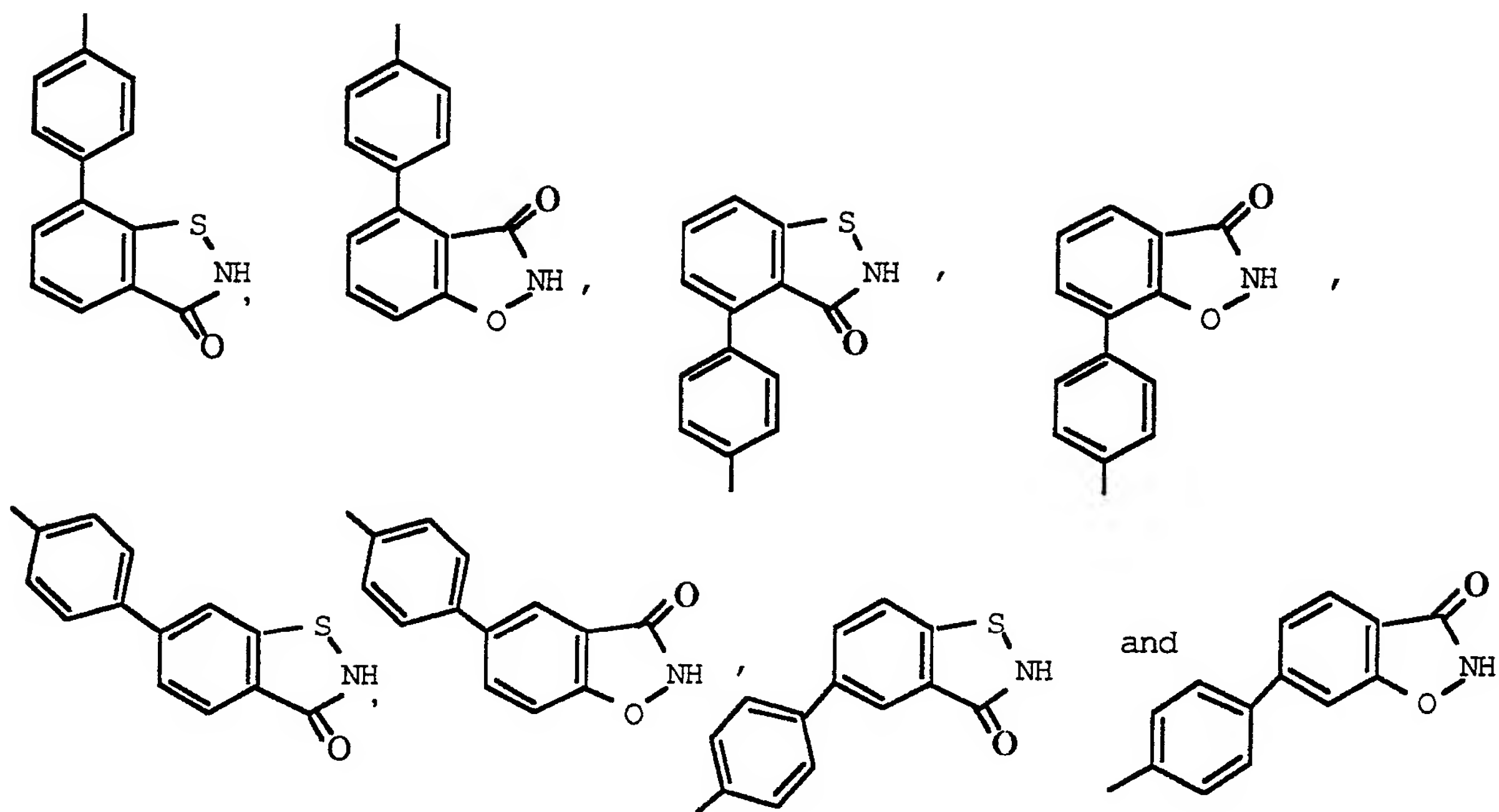


wherein each of R<sup>46</sup>, R<sup>47</sup> and R<sup>48</sup> is independently selected  
 5 from H, Cl, CN, NO<sub>2</sub>, CF<sub>3</sub>, C<sub>2</sub>F<sub>5</sub>, C<sub>3</sub>F<sub>7</sub>, CHF<sub>2</sub>, CH<sub>2</sub>F, CO<sub>2</sub>CH<sub>3</sub>,  
 CO<sub>2</sub>C<sub>2</sub>H<sub>5</sub>, SO<sub>2</sub>CH<sub>3</sub>, SO<sub>2</sub>CF<sub>3</sub> and SO<sub>2</sub>C<sub>6</sub>F<sub>5</sub>; wherein Z is selected  
 from O, S, NR<sup>49</sup> and CH<sub>2</sub>; wherein R<sup>49</sup> is selected from  
 hydrido, CH<sub>3</sub> and CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>; and wherein said acidic moiety  
 may be a heterocyclic acidic group attached at any two  
 10 adjacent positions of R<sup>3</sup> through R<sup>11</sup> so as to form a fused  
 ring system so as to include one of the phenyl rings of the  
 biphenyl moiety of Formula I, said biphenyl fused ring  
 system selected from

SUBSTITUTE SHEET


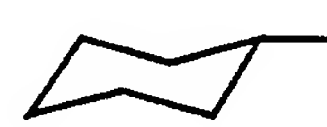
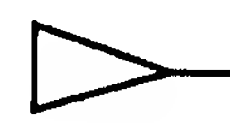


333



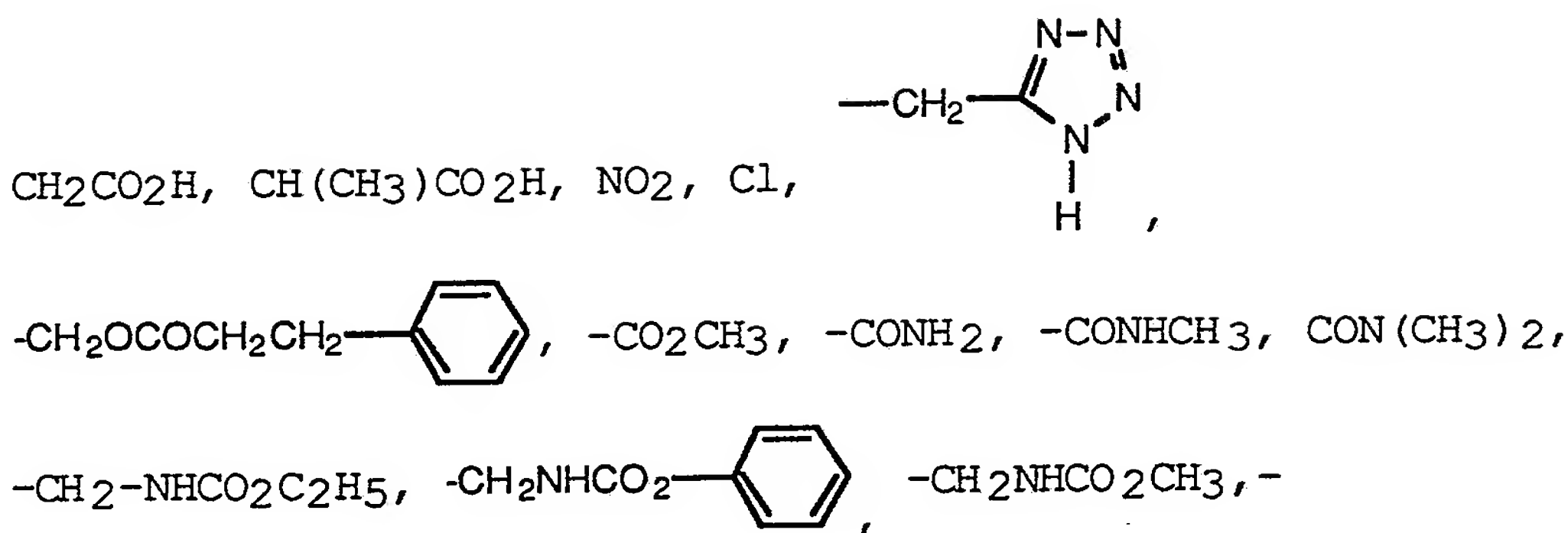
and the esters, amides and salts of said acidic moieties;

- 5 with the proviso that at least one of said  $R^1$  through  $R^{24}$  substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;
- 10 or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

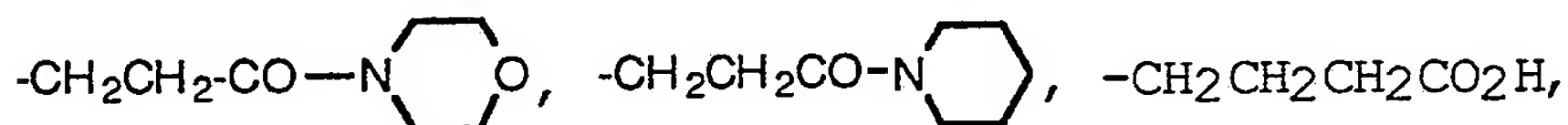
51. The composition of Claim 50 wherein m is one; wherein  $R^0$  is selected from  $C_4H_9(n)$ ,  $CH_3CH_2CH=CH$ ,  $C_3H_7(N)$ ,  $SC_3H_7$ , , ,  $C_2H_5$ ,  $C_5H_{11}(n)$ ,  $C_6H_{13}(n)$ ,  $SC_4H_9$ , ,  $CH_3CH=CH$  and  $CH_3CH_2CH_2CH=CH$ ;
- 15 wherein each of  $R^1$  and  $R^2$  is independently selected from amino, aminomethyl, aminoethyl, aminopropyl,  $CH_2OH$ ,  $CH_2OCOCH_3$ ,  $CH_2Cl$ ,  $Cl$ ,  $CH_2OCH_3$ ,  $CH_2OCH(CH_3)_2$ ,  $I$ ,  $CHO$ ,

**SUBSTITUTE SHEET**

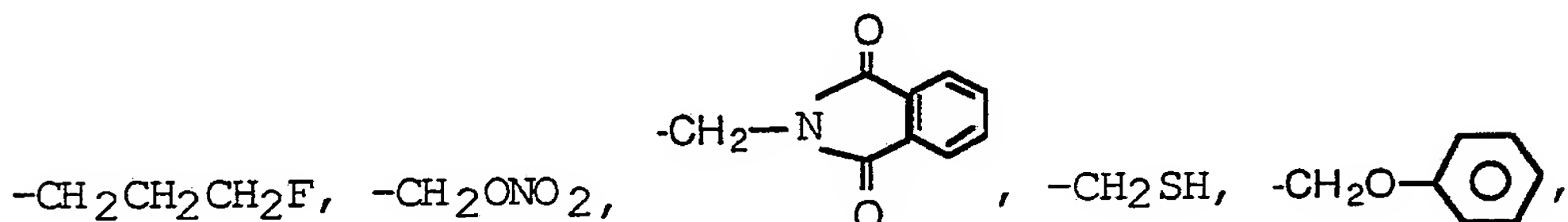
334

CH<sub>2</sub>NHCO<sub>2</sub>C<sub>3</sub>H<sub>7</sub>,

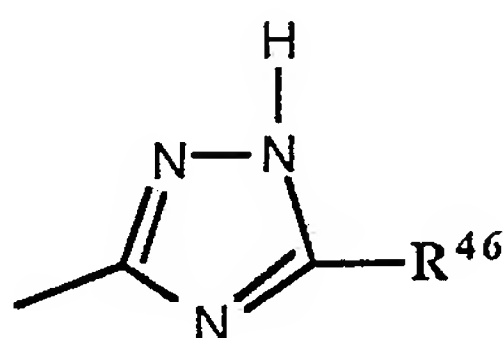
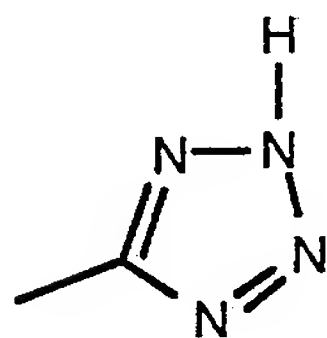
- 5 -CH<sub>2</sub>NHCO<sub>2</sub>CH<sub>2</sub>(CH<sub>3</sub>)<sub>2</sub>, -CH<sub>2</sub>NHCO<sub>2</sub>C<sub>4</sub>H<sub>9</sub>, CH<sub>2</sub>NHCO<sub>2</sub>-adamantyl,  
 -CH<sub>2</sub>NHCO<sub>2</sub>-(1-naphthyl), -CH<sub>2</sub>NHCONHCH<sub>3</sub>, -CH<sub>2</sub>NHCONHC<sub>2</sub>H<sub>5</sub>,  
 -CH<sub>2</sub>NHCONHC<sub>3</sub>H<sub>7</sub>, -CH<sub>2</sub>NHCONHC<sub>4</sub>H<sub>9</sub>, -CH<sub>2</sub>NHCONHCH(CH<sub>3</sub>)<sub>2</sub>,  
 -CH<sub>2</sub>NHCONH(1-naphthyl), -CH<sub>2</sub>NHCONH(1-adamantyl), CO<sub>2</sub>H,



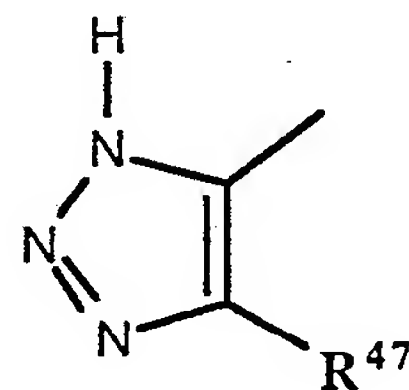
- 10 -CH<sub>2</sub>CH<sub>2</sub>F, -CH<sub>2</sub>OCONHCH<sub>3</sub>, -CH<sub>2</sub>OCSNHCH<sub>3</sub>, -CH<sub>2</sub>NHCSOC<sub>3</sub>H<sub>7</sub>,



52. Cl, NO<sub>2</sub>, CF<sub>3</sub>, CH<sub>2</sub>OH, Br, F, I, methyl, ethyl, n-propyl,  
 isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-  
 pentyl, isopentyl, neopentyl, phenyl, benzyl, phenethyl,  
 15 cyclohexyl, cyclohexylmethyl, 1-oxoethyl, 1-oxopropyl, 1-  
 oxobutyl, 1-oxopentyl, 1,1-dimethoxypropyl, 1,1-  
 dimethoxybutyl, 1,1-dimethoxypentyl, hydroxyalkyl, halo,  
 difluoromethyl, 1,1-difluoroethyl, 1,1-difluoropropyl, 1,1-  
 difluorobutyl and 1,1-difluoropentyl; wherein each of R<sup>3</sup>  
 20 through <sup>11</sup> is hydrido, with the proviso that at least one  
 of R<sup>5</sup>, R<sup>6</sup>, R<sup>8</sup> and R<sup>9</sup> is an acidic group selected from CO<sub>2</sub>H,  
 SH, PO<sub>3</sub>H<sub>2</sub>, SO<sub>3</sub>H, CONHNH<sub>2</sub>, CONHNHSO<sub>2</sub>CF<sub>3</sub>, OH,



and





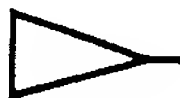



25

**SUBSTITUTE SHEET**

wherein each of  $R^{46}$  and  $R^{47}$  is independently selected from Cl, CN,  $NO_2$ ,  $CF_3$ ,  $CO_2CH_3$  and  $SO_2CF_3$ ;

5 with the proviso that at least one of said  $R^1$  through  $R^{11}$  substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

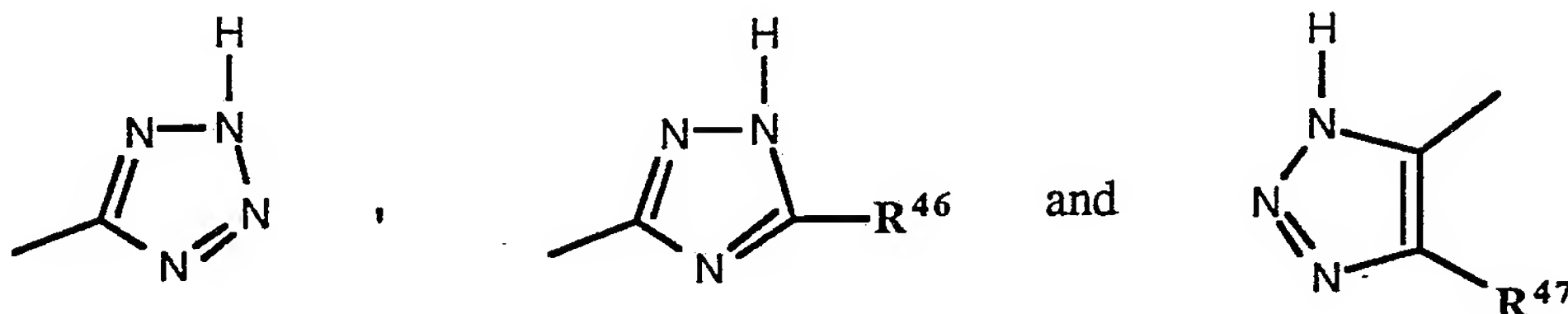
10 or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

52. The composition of Claim 51 wherein m is one; wherein  $R^0$  is selected from  $C_4H_9(n)$ ,  $CH_3CH_2CH=CH$ ,  $C_3H_7(N)$ ,  $SC_3H_7$ , , ,  $C_2H_5$ ,  $C_5H_{11}(n)$ ,   
 15  $C_6H_{13}(n)$ ,  $SC_4H_9$ , - $CH_2S$ ,  $CH_3CH=CH$  and  $CH_3CH_2CH_2CH=CH$ -; wherein  $R^1$  is selected from amino, aminomethyl, aminoethyl, aminopropyl,  $CH_2OH$ ,  $CH_2OCOCH_3$ ,  $CH_2Cl$ , Cl,  $CH_2OCH_3$ ,  $CH_2OCH(CH_3)_2$ , I, CHO,  $CH_2CO_2H$ ,  $CH(CH_3)CO_2H$ ,  $-CO_2CH_3$ ,  $-CONH_2$ ,  $-CONHCH_3$ ,  $CON(CH_3)_2$ ,   
 20  $-CH_2-NHCO_2C_2H_5$ ,  $-CH_2NHCO_2$ -,  $-CH_2NHCO_2CH_3$ ,  $-CH_2NHCO_2C_3H_7$ ,  $-CH_2NHCO_2CH_2(CH_3)_2$ ,  $-CH_2NHCO_2C_4H_9$ ,  $CH_2NHCO_2$ -adamantyl,  $-CH_2NHCO_2$ -(1-naphthyl),  $-CH_2NHCONHCH_3$ ,  $-CH_2NHCONHC_2H_5$ ,  $-CH_2NHCONHC_3H_7$ ,  $-CH_2NHCONHC_4H_9$ ,  $-CH_2NHCONHCH(CH_3)_2$ ,  $-CH_2NHCONH$ (1-naphthyl),  $-CH_2NHCONH$ (1-   
 25 adamantyl),  $CO_2H$ ,  $-CH_2CH_2CO-N$ ,  $-CH_2CH_2CH_2CO_2H$ ,  $-CH_2CH_2F$ ,  $-CH_2OCONHCH_3$ ,  $-CH_2CH_2CH_2F$ ,  $-CH_2SH$  and  $-CH_2O$ -; wherein  $R^2$  is selected from H, Cl,  $NO_2$ ,  $CF_3$ ,  $CH_2OH$ , Br, F, I, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, neopentyl,   
 30 phenyl, benzyl, phenethyl, cyclohexyl, cyclohexylmethyl, 1-oxoethyl, 1-oxopropyl, 1-oxobutyl, 1-oxopentyl, 1,1-dimethoxypropyl, 1,1-dimethoxybutyl, 1,1-dimethoxypentyl, hydroxyalkyl, halo, difluoromethyl, 1,1-difluoroethyl, 1,1-difluoropropyl, 1,1-difluorobutyl and 1,1-difluoropentyl;

336

wherein each of  $R^3$  through  $R^{11}$  is hydrido, with the proviso that at least one of  $R^5$ ,  $R^6$ ,  $R^8$  and  $R^9$  is an acidic group selected from  $CO_2H$ ,  $SH$ ,  $PO_3H_2$ ,  $SO_3H$ ,  $CONHNH_2$ ,  $CONHNHSO_2CF_3$ ,  $OH$ ,

5




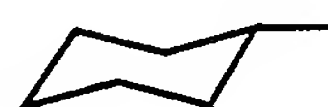
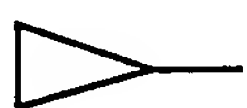
wherein each of  $R^{46}$  and  $R^{47}$  is independently selected from  $Cl$ ,  $CN$ ,  $NO_2$ ,  $CF_3$ ,  $CO_2CH_3$  and  $SO_2CF_3$ ;

10

with the proviso that at least one of said  $R^1$  through  $R^{11}$  substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

15

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.


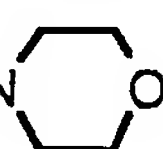

53. The composition of Claim 51 wherein  $m$  is one; wherein  $R^0$  is selected from  $C_4H_9(n)$ ,  $CH_3CH_2CH=CH$ ,  $C_3H_7(N)$ ,  $SC_3H_7$ , , ,  $C_2H_5$ ,  $C_5H_{11}(n)$ ,  $C_6H_{13}(n)$ ,  $SC_4H_9$ , ,  $CH_3CH=CH$  and  $CH_3CH_2CH_2CH=CH$ ;

wherein  $R^1$  is selected from  $H$ ,  $Cl$ ,  $NO_2$ ,  $CF_3$ ,  $CH_2OH$ ,  $Br$ ,  $F$ ,  $I$ , methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, neopentyl, phenyl, benzyl, phenethyl, cyclohexyl, cyclohexylmethyl, 1-oxoethyl, 1-oxopropyl, 1-oxobutyl, 1-oxopentyl, 1,1-dimethoxypropyl, 1,1-dimethoxybutyl, 1,1-dimethoxypentyl, hydroxyalkyl, halo, difluoromethyl, 1,1-difluoroethyl, 1,1-difluoropropyl, 1,1-difluorobutyl and 1,1-difluoropentyl; wherein  $R^2$  is selected from amino, aminomethyl, aminoethyl,

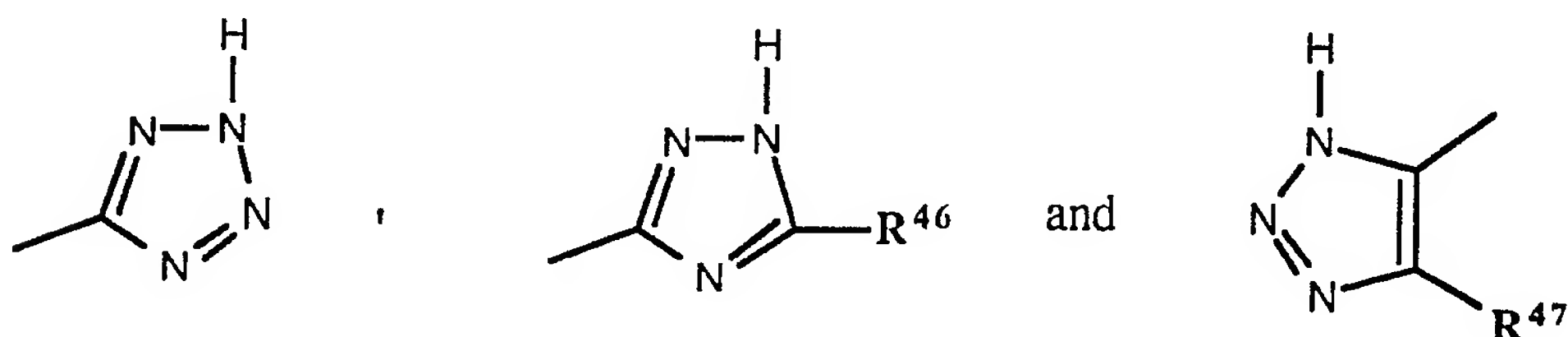
**SUBSTITUTE SHEET**

337

aminopropyl,  $\text{CH}_2\text{OH}$ ,  $\text{CH}_2\text{OCOCH}_3$ ,  $\text{CH}_2\text{Cl}$ ,  $\text{Cl}$ ,  $\text{CH}_2\text{OCH}_3$ ,  
 $\text{CH}_2\text{OCH}(\text{CH}_3)_2$ ,  $\text{I}$ ,  $\text{CHO}$ ,  
 $\text{CH}_2\text{CO}_2\text{H}$ ,  $\text{CH}(\text{CH}_3)\text{CO}_2\text{H}$ ,  $-$ ,  $-\text{CO}_2\text{CH}_3$ ,  $-\text{CONH}_2$ ,  $-\text{CONHCH}_3$ ,  
 $\text{CON}(\text{CH}_3)_2$ ,

- 5  $-\text{CH}_2-\text{NHCO}_2\text{C}_2\text{H}_5$ ,  $-\text{CH}_2\text{NHCO}_2-$  ,  $-\text{CH}_2\text{NHCO}_2\text{CH}_3$ ,  $-$   
 $\text{CH}_2\text{NHCO}_2\text{C}_3\text{H}_7$ ,  
 $-\text{CH}_2\text{NHCO}_2\text{CH}_2(\text{CH}_3)_2$ ,  $-\text{CH}_2\text{NHCO}_2\text{C}_4\text{H}_9$ ,  $\text{CH}_2\text{NHCO}_2$ -adamantyl,  
 $-\text{CH}_2\text{NHCO}_2$ -(1-naphthyl),  $-\text{CH}_2\text{NHCONHCH}_3$ ,  $-\text{CH}_2\text{NHCONHC}_2\text{H}_5$ ,  
 $-\text{CH}_2\text{NHCONHC}_3\text{H}_7$ ,  $-\text{CH}_2\text{NHCONHC}_4\text{H}_9$ ,  $-\text{CH}_2\text{NHCONHCH}(\text{CH}_3)_2$ ,  
10  $-\text{CH}_2\text{NHCONH}$ (1-naphthyl),  $-\text{CH}_2\text{NHCONH}$ (1-adamantyl),  $\text{CO}_2\text{H}$ ,  
 $-\text{CH}_2\text{CH}_2-\text{CO}-\text{N}$  ,  $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$ ,  $-\text{CH}_2\text{CH}_2\text{F}$ ,  $-\text{CH}_2\text{OCONHCH}_3$ ,  $-$   
 $\text{CH}_2\text{CH}_2\text{CH}_2\text{F}$ ,  $-\text{CH}_2\text{SH}$  and  $-\text{CH}_2\text{O}-$  ;

- wherein each of  $\text{R}^3$  through  $11$  is hydrido, with the proviso  
that at least one of  $\text{R}^5$ ,  $\text{R}^6$ ,  $\text{R}^8$  and  $\text{R}^9$  is an acidic group  
15 selected from  $\text{CO}_2\text{H}$ ,  $\text{SH}$ ,  $\text{PO}_3\text{H}_2$ ,  $\text{SO}_3\text{H}$ ,  $\text{CONHNH}_2$ ,  $\text{CONHNHSO}_2\text{CF}_3$ ,  
 $\text{OH}$ ,



- 20 wherein each of  $\text{R}^{46}$  and  $\text{R}^{47}$  is independently selected from  
 $\text{Cl}$ ,  $\text{CN}$ ,  $\text{NO}_2$ ,  $\text{CF}_3$ ,  $\text{CO}_2\text{CH}_3$  and  $\text{SO}_2\text{CF}_3$ ;

- with the proviso that at least one of said  $\text{R}^1$  through  $\text{R}^{11}$   
substituents contains a terminal primary or secondary amino  
25 moiety or a moiety convertible to a primary or secondary  
amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt  
thereof.

30

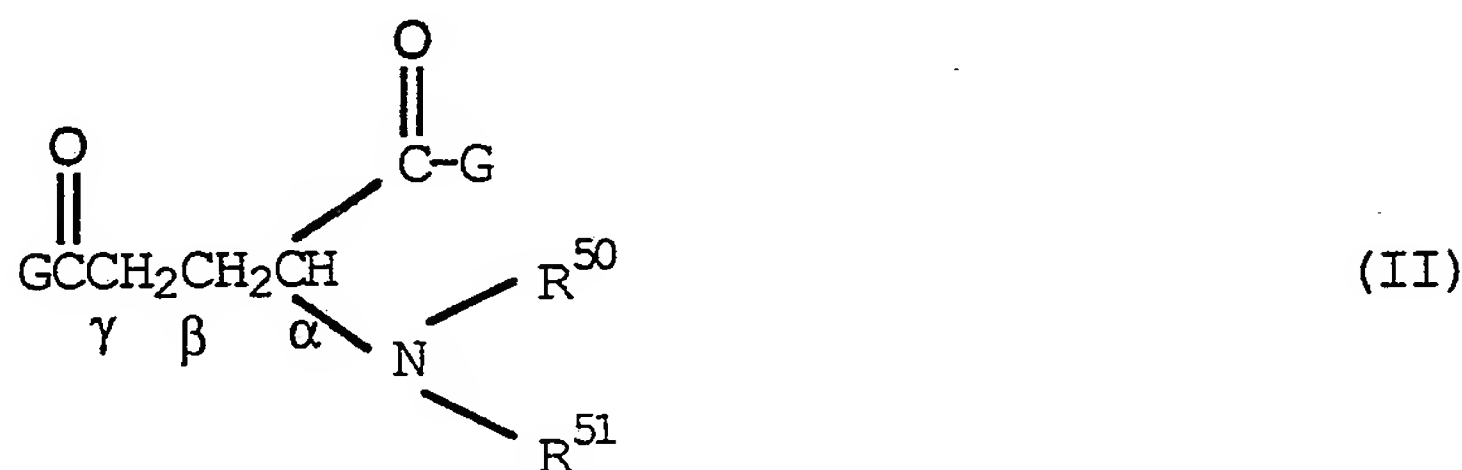
54. The composition of Claim 43 wherein said  
second residue forms a kidney-enzyme-cleavable amide bond

SUBSTITUTE SHEET

338

with the residue of said angiotensin II antagonist compound.

55. The composition of Claim 54 wherein said  
5 second residue is provided by a compound of Formula II:



10 wherein each of  $\text{R}^{50}$  and  $\text{R}^{51}$  may be independently selected from hydrido, alkylcarbonyl, alkoxy carbonyl, alkoxyalkyl, hydroxyalkyl and haloalkyl; and wherein G is selected from hydroxyl, halo, mercapto,  $-\text{OR}^{52}$ ,  $-\text{SR}^{53}$  and  
 $\begin{array}{c} \diagup \\ \diagdown \end{array} \text{NR}^{54}$  with each of  $\text{R}^{52}$ ,  $\text{R}^{53}$  and  $\text{R}^{54}$  independently  
 15 selected from hydrido and alkyl; with the proviso that said Formula II compound is selected such that formation of the cleavable amide bond occurs at carbonyl moiety attached at the gamma-position carbon of said Formula II compound.

56. The composition of Claim 55 wherein each G  
20 substituent is hydroxy.

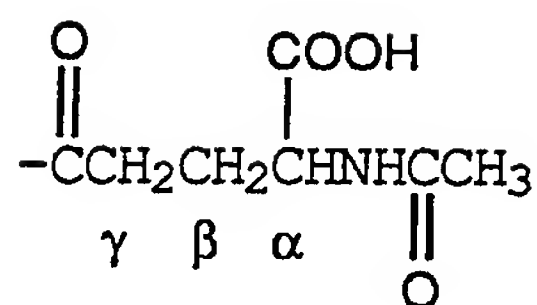
57. The composition of Claim 56 wherein each G  
substituent is hydroxy; wherein  $\text{R}^{50}$  is hydrido; and wherein  
 25  $\text{R}^{51}$  is selected from

$\begin{array}{c} \text{O} \\ \parallel \\ -\text{CR}^{55} \end{array}$  wherein  $\text{R}^{55}$  is selected from methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, neopentyl, n-hexyl and chloromethyl.

58. The composition of Claim 57 wherein said  
30 second residue is

**SUBSTITUTE SHEET**

339

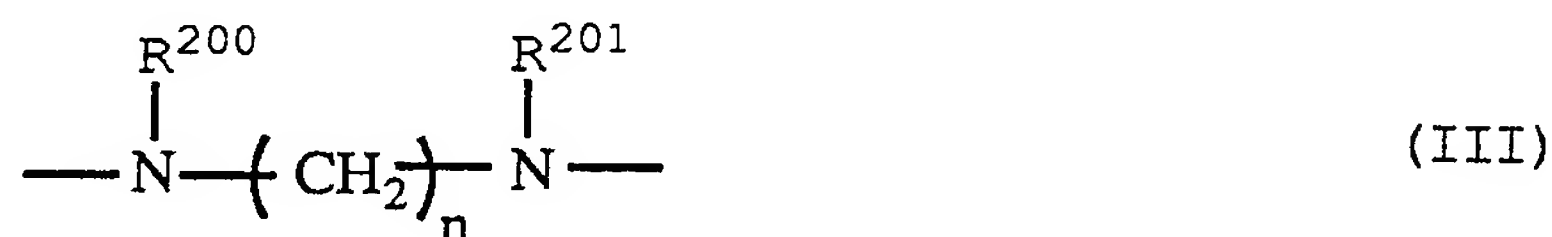


59. The composition of Claim 43 wherein said first residue is an angiotensin II antagonist compound  
 5 containing a terminal primary or secondary amino moiety selected from amino and linear or branched aminoalkyl moieties containing linear or branched alkyl groups selected from aminomethyl, aminoethyl, aminopropyl, aminoisopropyl, aminobutyl, aminosecbutyl, aminoisobutyl,  
 10 aminotertbutyl, aminopentyl, aminoisopentyl and aminoneopentyl.

60. The composition of Claim 43 wherein said first residue is an angiotensin II antagonist compound  
 15 containing a moiety convertible to a primary or secondary amino terminal moiety.

61. The composition of Claim 60 wherein said moiety convertible to an amino terminal moiety is a  
 20 carboxylic acid group reactable with an amino moiety of a diamino-terminated linker group to provide a terminal amino moiety which may then be further reacted with a carboxylic acid moiety of a compound providing said second residue so as to form a hydrolyzable amide bond.

25 62. The composition of Claim 61 wherein said diamino-terminated linker group is a divalent radical of Formula III:



30 wherein each of  $\text{R}^{200}$  and  $\text{R}^{201}$  may be independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, alkoxyalkyl, hydroxyalkyl, aralkyl, aryl, haloalkyl, amino,

**SUBSTITUTE SHEET**

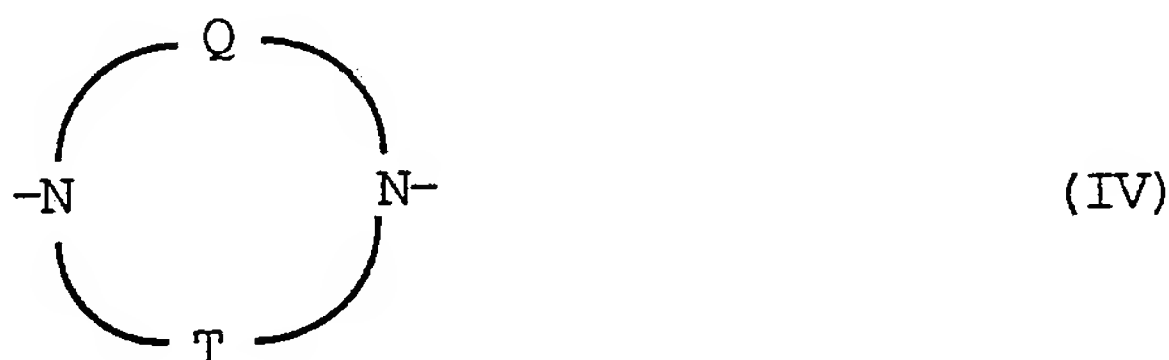


monoalkylamino, dialkylamino, cyanoamino, carboxyalkyl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; and wherein n is zero or a number selected from three through seven, inclusive.

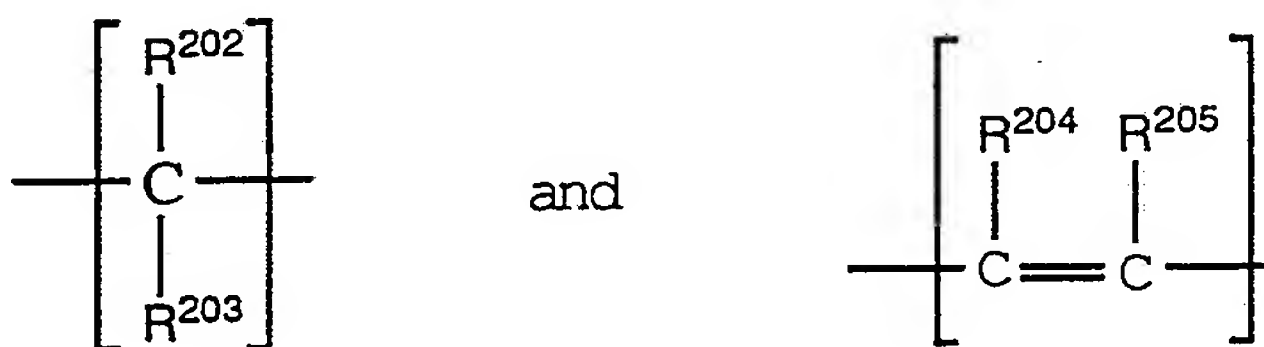
5

63. The composition of Claim 62 wherein each of R<sup>200</sup> and R<sup>201</sup> is hydrido.

64. The composition of Claim 61 wherein said  
10 diamino-terminated linker group is a divalent radical of Formula IV:



15 wherein each of Q and T is one or more groups independently selected from

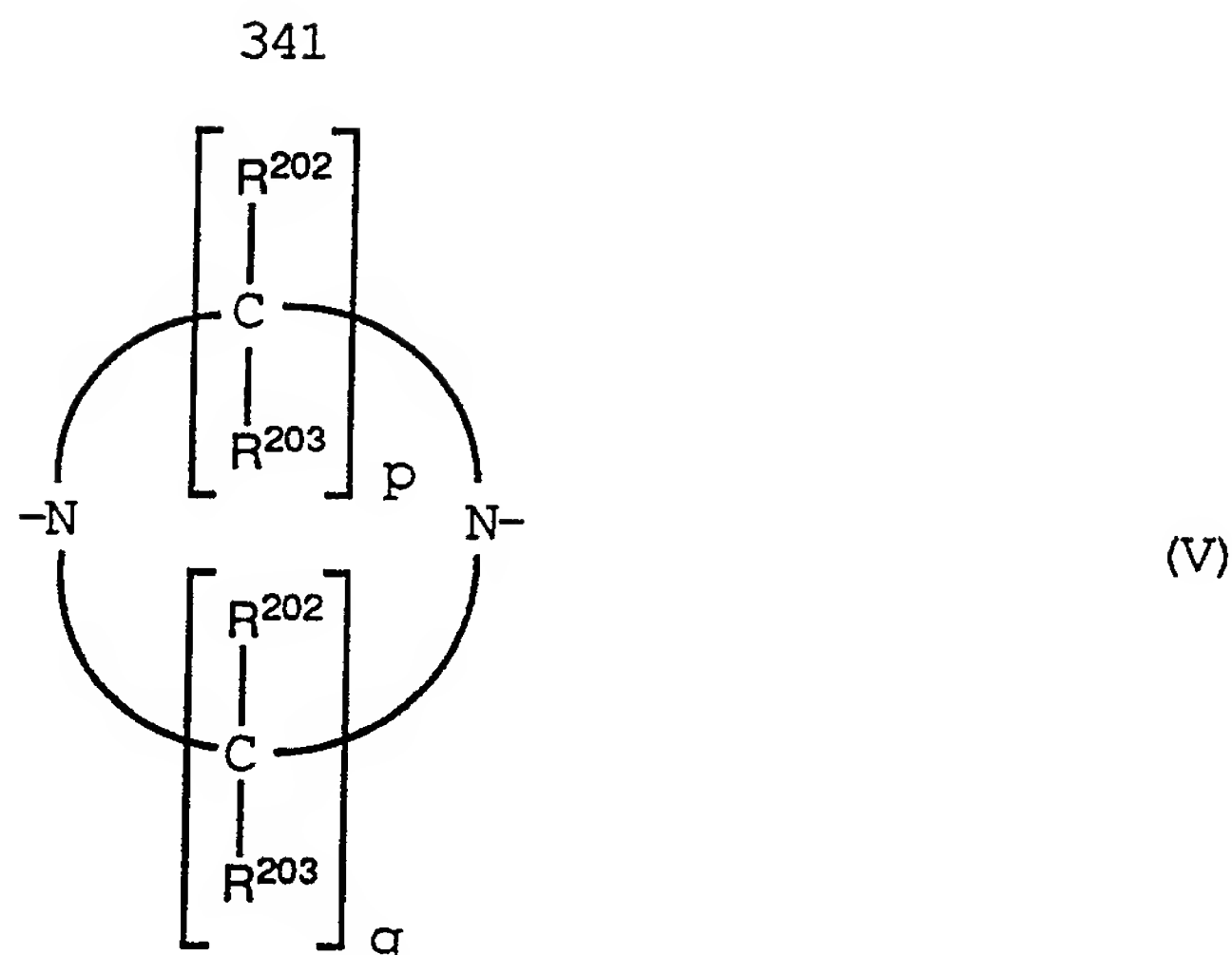


20 wherein each of R<sup>202</sup> through R<sup>205</sup> is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, aryloxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl,  
25 alkanoyl, alkenyl, cycloalkenyl and alkynyl.

65. The composition of Claim 64 wherein said  
diamino-terminated linker group is a divalent radical of  
Formula V:

30





wherein each of  $R^{202}$  and  $R^{203}$  is independently selected from hydrido, hydroxy, alkyl, phenalkyl, phenyl, alkoxy, benzyloxy, phenoxy, alkoxyalkyl, hydroxyalkyl, halo, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl and alkanoyl; and wherein each of  $p$  and  $q$  is a number independently selected from one through six, inclusive; with the proviso that when each of  $R^{202}$  and  $R^{203}$  is selected from halo, hydroxy, amino, monoalkylamino and dialkylamino, then the carbon to which  $R^{202}$  or  $R^{203}$  is attached in Formula V is not adjacent to a nitrogen atom of Formula V.

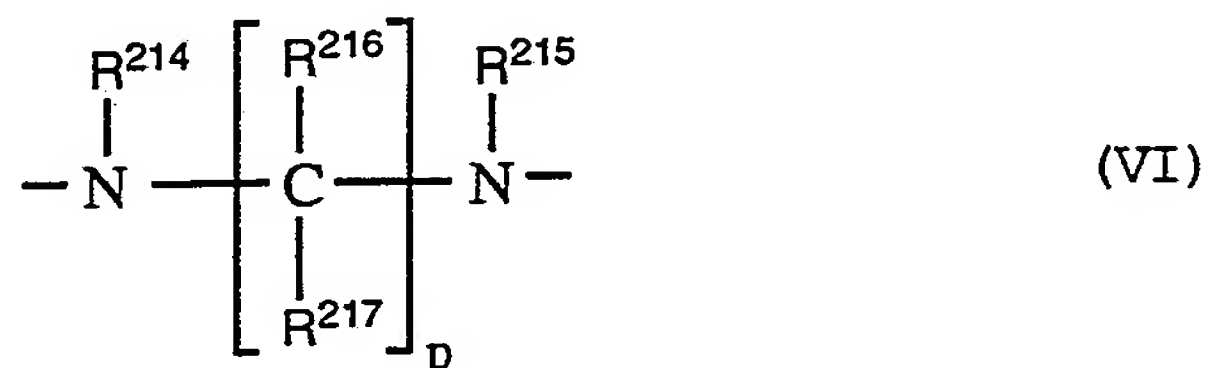
66. The composition of Claim 65 wherein each of  $R^{202}$  and  $R^{203}$  is independently selected from hydrido, hydroxy, alkyl, alkoxy, amino, monoalkylamino, carboxy, carboxyalkyl and alkanoyl; and wherein each of  $p$  and  $q$  is a number independently selected from two through four, inclusive.

67. The composition of Claim 66 wherein each of  $R^{202}$  and  $R^{203}$  is independently selected from hydrido, amino, monoalkylamino and carboxyl; and wherein each of  $p$  and  $q$  is independently selected from the numbers two and three.

68. The composition of Claim 67 wherein each of  $R^{202}$  and  $R^{203}$  is hydrido; and wherein each of  $p$  and  $q$  is two.

**SUBSTITUTE SHEET**

69. The composition of Claim 61 wherein said diamino-terminated linker group is a divalent radical of Formula VI:



wherein each of R<sup>214</sup> through R<sup>217</sup> is independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, hydroxyalkyl, alkoxyalkyl, aralkyl, aryl, haloalkyl, amino, monoalkylamino, dialkylamino, cyanoamino, carboxyalkyl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; and wherein p is a number selected from one through six inclusive.

70. The composition of Claim 69 wherein each of R<sup>214</sup> and R<sup>215</sup> is hydrido; wherein each of R<sup>216</sup> and R<sup>217</sup> is independently selected from hydrido, alkyl, phenalkyl, phenyl, alkoxyalkyl, hydroxyalkyl, haloalkyl and carboxyalkyl; and wherein p is two or three.

71. The composition of Claim 70 wherein each of R<sup>214</sup> and R<sup>215</sup> is hydrido; wherein each of R<sup>216</sup> and R<sup>217</sup> is independently selected from hydrido and alkyl; and wherein p is two.

72. The composition of Claim 71 wherein each of R<sup>214</sup>, R<sup>215</sup>, R<sup>216</sup> and R<sup>217</sup> is hydrido; and wherein p is two.

73. The composition of Claim 52 wherein said angiotensin II antagonist compound is 4'-[2-butyl-5-chloro-4-(hydroxymethyl)-1H-imidazol-1-ylmethyl][1,1'-biphenyl]-2-carboxylic acid.

74. The composition of Claim 73 wherein said conjugate is N-acetyl-L-glutamic acid, 5-[[4'-[2-butyl-5-chloro-4-(hydroxymethyl)-1H-imidazol-1-ylmethyl][1,1'-biphenyl]-2-yl]carbonyl]hydrazide.

75. The composition of Claim 73 wherein said conjugate is N<sup>2</sup>-acetyl-N-[[2-butyl-5-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazol-4-yl]methyl]-L-glutamine.

76. The composition of Claim 73 which is N-acetyl-L-glutamic acid, 5-[2-butyl-5-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazol-4-yl]acetylhydrazide.

77. The composition of Claim 53 wherein said angiotensin II antagonist compound is 4'-[2-butyl-4-chloro-5-(hydroxymethyl)-1H-imidazol-1-ylmethyl][1,1'-biphenyl]-2-carboxylic acid.

78. The composition of Claim 77 which is N-acetyl-L-glutamic acid, 5-[[4'-[2-butyl-4-chloro-5-(hydroxymethyl)-1H-imidazol-1-ylmethyl][1,1'-biphenyl]-2-yl]carbonyl]hydrazide.

79. The composition of Claim 77 which is N<sup>2</sup>-acetyl-N-[[2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazol-5-yl]methyl]-L-glutamine.

80. The composition of Claim 77 which is N-acetyl-L-glutamic acid, 5-[2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazol-5-yl]acetylhydrazide.

81. A method for treating a hypertensive-related disorder or a sodium-retaining disorder, said method comprising administering to a patient afflicted with

or susceptible to said disorder a therapeutically-effective amount of a renal-selective conjugate, said conjugate comprising a residue of an angiotensin II antagonist compound.

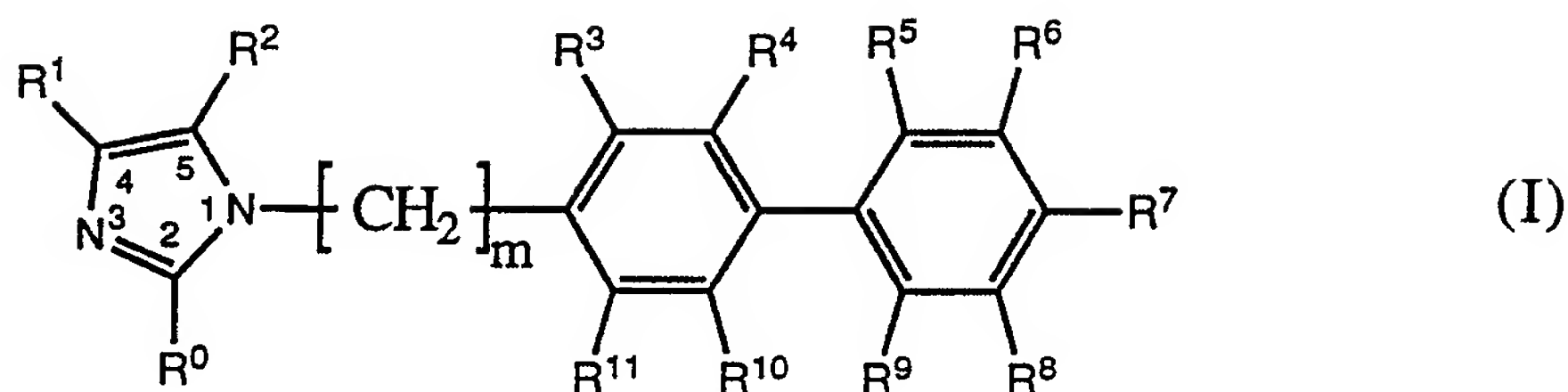
5

82. The method of Claim 81 wherein said conjugate comprises a first residue and a second residue, said first and second residues connected together by a cleavable bond, wherein said first residue is provided by an angiotensin II antagonist compound, and wherein said second residue is capable of being cleaved from said first residue.

83. The method of Claim 82 wherein said first and second residues are provided by precursor compounds wherein the precursor compound of one of said first and second residues has a reactable carboxylic acid moiety and the precursor of the other of said first and second residues has a reactable amino moiety or a moiety convertible to a reactable amino moiety, whereby a cleavable bond may be formed between said carboxylic acid moiety and said amino moiety.

84. The method of Claim 83 wherein said angiotensin II antagonist compound providing said first residue is selected from biphenylmethyl 1H-substituted-1,3-imidazole compounds.

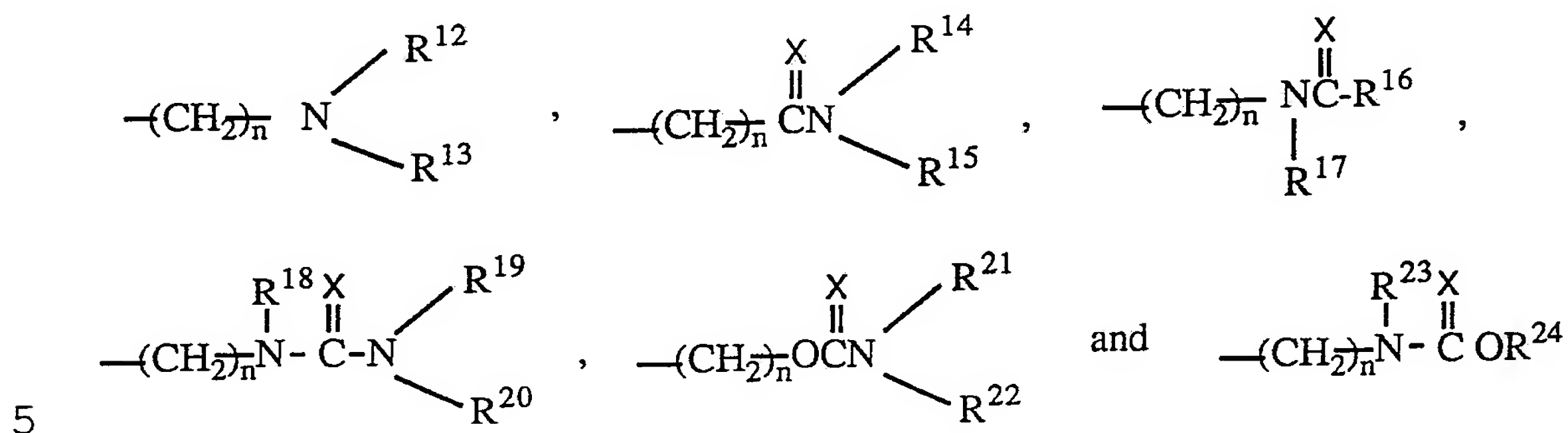
85. The method of Claim 84 wherein said angiotensin II antagonist compound is selected from a class of compounds defined by Formula I:



wherein m is a number selected from one to four, inclusive;

- 5 wherein each of R<sup>0</sup> through R<sup>11</sup> is independently selected from hydrido, alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, formyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkylcarbonylalkyl, alkoxycarbonyl, alkenyl, 10 cycloalkenyl, alkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, mercaptocarbonyl, mercaptothiocarbonyl, mercaptoalkyl, alkoxycarbonyloxy, 15 alkylthio, cycloalkylthio, alkylthiocarbonyl, alkylcarbonylthio, alkylthiocarbonyloxy, alkylthiocarbonylthio, alkylthiothiocarbonyl, alkylthiothiocarbonylthio, arylthio, arylthiocarbonyl, arylcarbonylthio, arylthiocarbonyloxy, 20 arylthiocarbonylthio, arylthiothiocarbonyl, arylthiothiocarbonylthio, aralkylthio, aralkylthiocarbonyl, aralkylcarbonylthio, aralkylthiocarbonyloxy, aralkylthiocarbonylthio, alkylthiocarbonyl, aralkylthiocarbonylthio, mercapto, alkylsulfinyl, 25 alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, phthalimido, phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and cycloheteroalkylcarbonylalkyl wherein each of said heteroaryl- and cyclohetero-containing 30 groups has one or more ring atoms selected from oxygen,

sulfur and nitrogen atoms, and wherein each of  $R^0$  through  $R^{11}$  may be further independently selected from amino and amido radicals of the formula



wherein X is oxygen atom or sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

wherein each of  $R^{12}$  through  $R^{24}$  is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl, and wherein  $R^{12}$  and  $R^{13}$  taken together,  $R^{14}$  and  $R^{15}$  taken together,  $R^{16}$  and  $R^{17}$  taken together,  $R^{19}$  and  $R^{20}$  taken together and  $R^{21}$  and  $R^{22}$  taken together may each form a heterocyclic group having five to seven ring members including the nitrogen atom of said amino or amido radical and which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms and which heterocyclic group may be saturated or partially unsaturated; wherein  $R^{12}$  and  $R^{13}$  taken together,  $R^{14}$  and  $R^{15}$  taken together,  $R^{19}$  and  $R^{20}$  taken together and  $R^{21}$  and  $R^{22}$  taken together may each form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino or amido radical and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms;



and wherein each of  $R^3$  through  $R^{11}$  may be further independently selected from hydrido and haloalkyl, and from acidic moieties of the formula

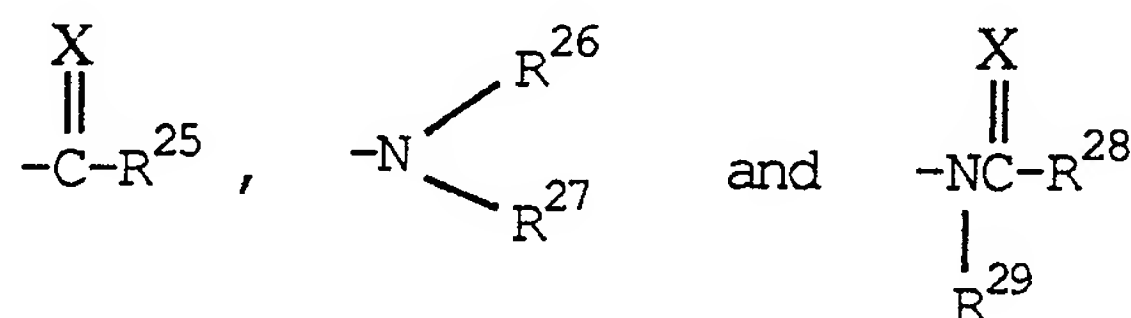
5



wherein n is a number selected from zero through three, inclusive, and wherein A is an acidic group selected to contain at least one acidic hydrogen atom, and the amide, ester and salt derivatives of said acidic moieties; wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aryl, aralkyl and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms;

and wherein any of the foregoing  $R^1$  through  $R^{24}$ , Y and A groups having a substitutable position may be substituted with one or more groups selected from hydroxy, alkyl, alkenyl, alkynyl, aralkyl, hydroxyalkyl, trifluoromethyl, difluoroalkyl, oxo, alkoxy, aryloxy, aralkoxy, aralkylthio, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, aroyl, cycloalkenyl, cyano, cyanoamino, nitro, alkylcarbonyloxy, alkoxy carbonyloxy, alkylcarbonyl, alkoxy carbonyl, carboxyl, mercapto, mercaptocarbonyl, alkylthio, arylthio, alkylthiocarbonyl, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms, and amino and amido radicals of the formula

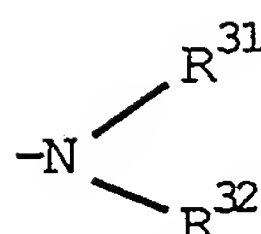
30



wherein X is selected from oxygen atom and sulfur atom; wherein  $R^{25}$  is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl,  $\text{DR}^{30}$  and

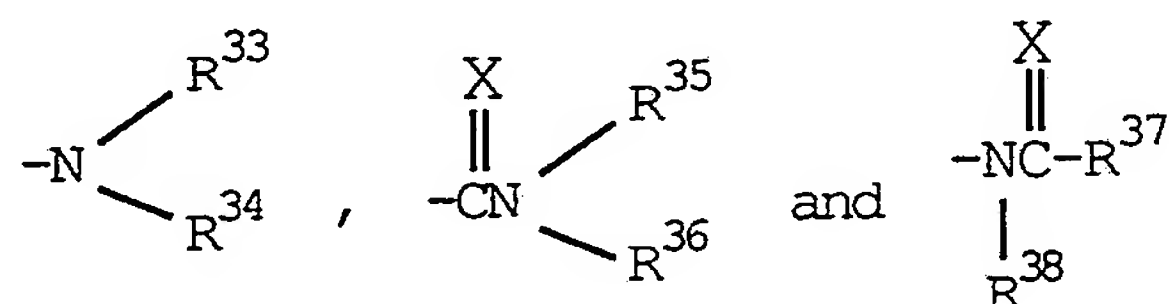
35

348



wherein D is selected from oxygen atom and sulfur atom and  
 5 R<sup>30</sup> is selected from hydrido, alkyl, cycloalkyl,  
 cycloalkylalkyl, aralkyl and aryl; wherein each of R<sup>25</sup>,  
 R<sup>26</sup>, R<sup>27</sup>, R<sup>28</sup>, R<sup>29</sup>, R<sup>31</sup> and R<sup>32</sup> is independently selected  
 from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl,  
 haloalkyl, cycloalkylalkyl, alkoxyalkyl, alkylcarbonyl,  
 10 alkoxycarbonyl, carboxyl, alkylsulfinyl, alkylsulfonyl,  
 arylsulfinyl, arylsulfonyl, haloalkylsulfinyl,  
 haloalkylsulfonyl, aralkyl and aryl, and wherein each of  
 R<sup>26</sup>, R<sup>27</sup>, R<sup>28</sup>, R<sup>29</sup>, R<sup>31</sup> and R<sup>32</sup> is further independently  
 selected from amino and amido radicals of the formula

15



wherein X is oxygen atom or sulfur atom;

20 wherein each of R<sup>33</sup>, R<sup>34</sup>, R<sup>35</sup>, R<sup>36</sup>, R<sup>37</sup> and R<sup>38</sup> is  
 independently selected from hydrido, alkyl, cycloalkyl,  
 cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl,  
 cycloalkylalkyl, alkoxyalkyl, haloalkylsulfinyl,  
 haloalkylsulfonyl, aralkyl and aryl, and wherein R<sup>26</sup> and  
 25 R<sup>27</sup> taken together and R<sup>28</sup> and R<sup>29</sup> taken together may each  
 form a heterocyclic group having five to seven ring members  
 including the nitrogen atom of said amino or amido radical,  
 which heterocyclic group may further contain one or more  
 hetero atoms as ring members selected from oxygen, nitrogen  
 30 and sulfur atoms and which heterocyclic group may be  
 saturated or partially unsaturated; wherein R<sup>26</sup> and R<sup>27</sup>  
 taken together and R<sup>31</sup> and R<sup>32</sup> taken together may each form  
 an aromatic heterocyclic group having five ring members  
 including the nitrogen atom of said amino or amido radical



and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms;

- 5 with the proviso that at least one of said R<sup>1</sup> through R<sup>24</sup>, Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;
- 10 or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

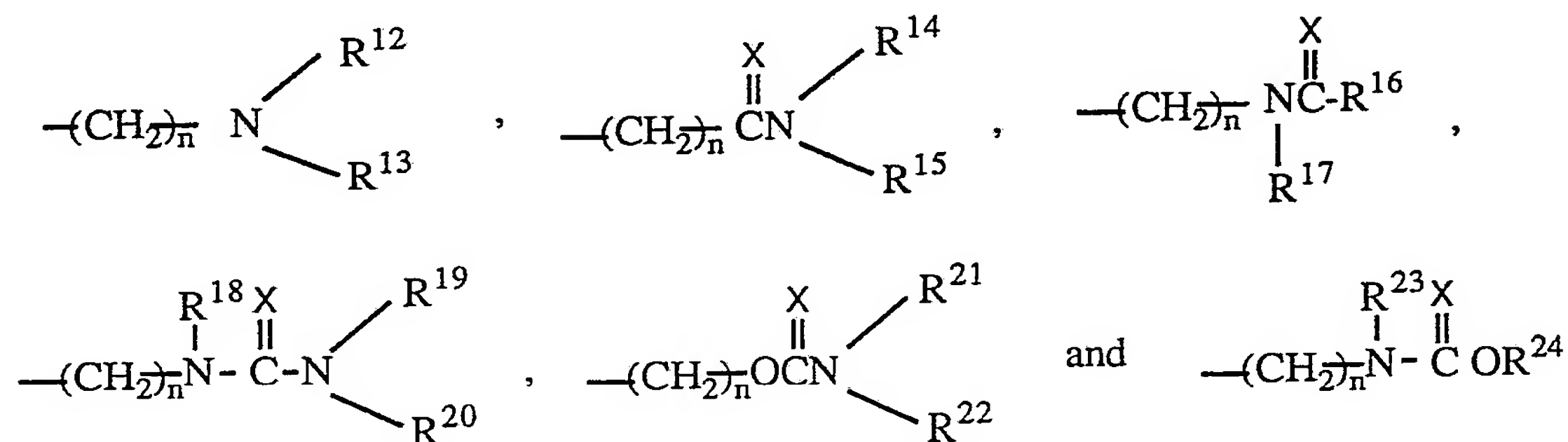
86. The method of Claim 85 wherein m is one; wherein each of R<sup>0</sup> through R<sup>11</sup> is independently selected
- 15 from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxy carbonyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, cyano, nitro, carboxyl, carboxyalkyl,
- 20 alkylcarbonyloxy, alkylcarbonyloxyalkyl, alkoxy carbonylalkyl, aralkoxy carbonylalkyl, aralkylcarbonyloxyalkyl, mercaptocarbonyl, mercaptothiocarbonyl, mercaptoalkyl, alkoxy carbonyloxy, alkylthio, cycloalkylthio, alkylthiocarbonyl,
- 25 alkylcarbonylthio, alkylthiocarbonyloxy, alkylthio-carbonylthio, alkylthiothiocarbonyl, alkylthiothio-carbonylthio, arylthio, arylthiocarbonyl, arylcarbonylthio, arylthiocarbonyloxy, arylthiocarbonylthio, arylthiothiocarbonyl, arylthiothiocarbonylthio,
- 30 aralkylthio, aralkylthiocarbonyl, aralkylcarbonylthio, aralkylthiocarbonyloxy, aralkylthiocarbonylthio, aralkylthiocarbonyl, aralkylthiocarbonylthio, mercapto, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, phthalimido,
- 35 phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and cycloheteroalkylcarbonylalkyl wherein each of said heteroaryl- and cycloheteroalkyl-containing groups has

**SUBSTITUTE SHEET**

350

one or more hetero ring atoms selected from oxygen, sulfur and nitrogen atoms, and wherein each of  $R^0$  through  $R^{11}$  may be further independently selected from amino and amido radicals of the formula

5



wherein X is selected from oxygen atom or sulfur atom;

10

wherein each n is a number independently selected from zero to six, inclusive;

wherein each of  $R^{12}$  through  $R^{24}$  is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl;

15

and wherein each of  $R^3$  through  $R^{11}$  may be further independently selected from hydrido and haloalkyl, and from acidic moieties of the formula

20



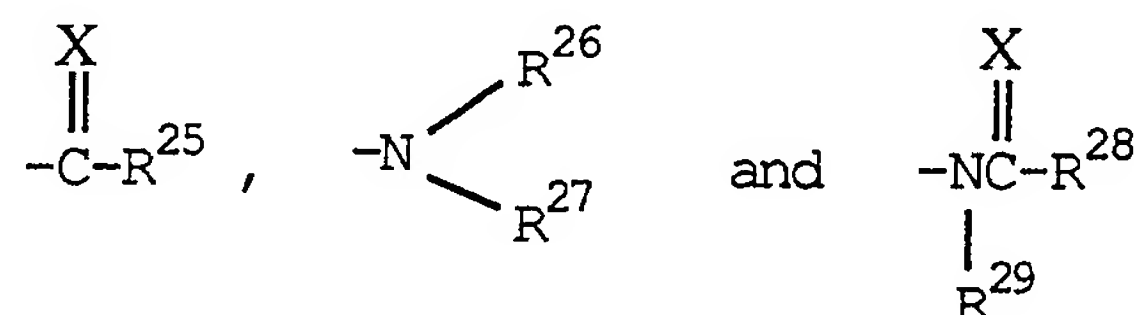
25

wherein n is a number selected from zero through three, inclusive; wherein A is an acidic group selected from acids containing one or more atoms selected from oxygen, sulfur, phosphorus and nitrogen atoms, and wherein said acidic group is selected to contain at least one acidic hydrogen atom, and the amide, ester and salt derivatives of said acidic moieties; wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl,

30

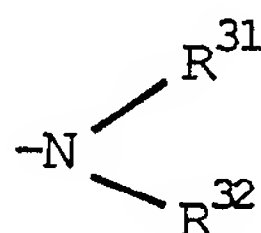
cycloalkylalkyl, alkenyl, alkynyl, aryl, aralkyl and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms;

- 5 and wherein any of the foregoing  $R^1$  through  $R^{24}$ , Y and A groups having a substitutable position may be substituted with one or more groups selected from alkyl, alkenyl, aralkyl, hydroxyalkyl, trifluoromethyl, difluoroalkyl, alkoxy, aryloxy, aralkoxy, alkoxyalkyl, alkylcarbonyl, 10 alkoxy carbonyl, carboxyl, mercaptocarbonyl, alkylthio, alkylthiocarbonyl, and amino and amido radicals of the formula



15

wherein X is selected from oxygen atom and sulfur atom; wherein  $R^{25}$  is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, and  $\text{DR}^{30}$  and

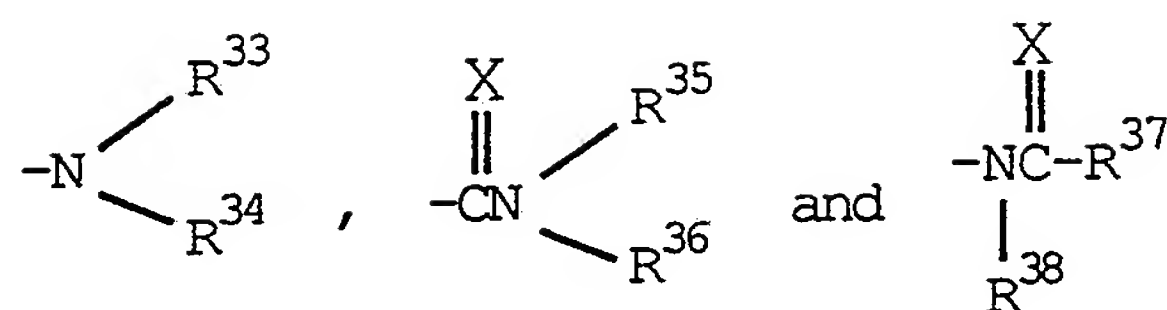


20

- wherein D is selected from oxygen atom and sulfur atom, and  $R^{30}$  is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl and aryl; wherein each of  $R^{26}$ , 25  $R^{27}$ ,  $R^{28}$ ,  $R^{29}$ ,  $R^{31}$  and  $R^{32}$  is independently selected from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, alkanoyl, alkoxy carbonyl, carboxyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl, and wherein each of  $R^{26}$ ,  $R^{27}$ ,  $R^{28}$ ,  $R^{29}$ ,  $R^{31}$  and  $R^{32}$  30 is further independently selected from amino and amido radicals of the formula

**SUBSTITUTE SHEET**

352



wherein X is selected from oxygen atom or sulfur atom;

- 5 wherein each of R<sup>26</sup> through R<sup>31</sup> is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl;

10

with the proviso that at least one of said R<sup>1</sup> through R<sup>24</sup>, Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

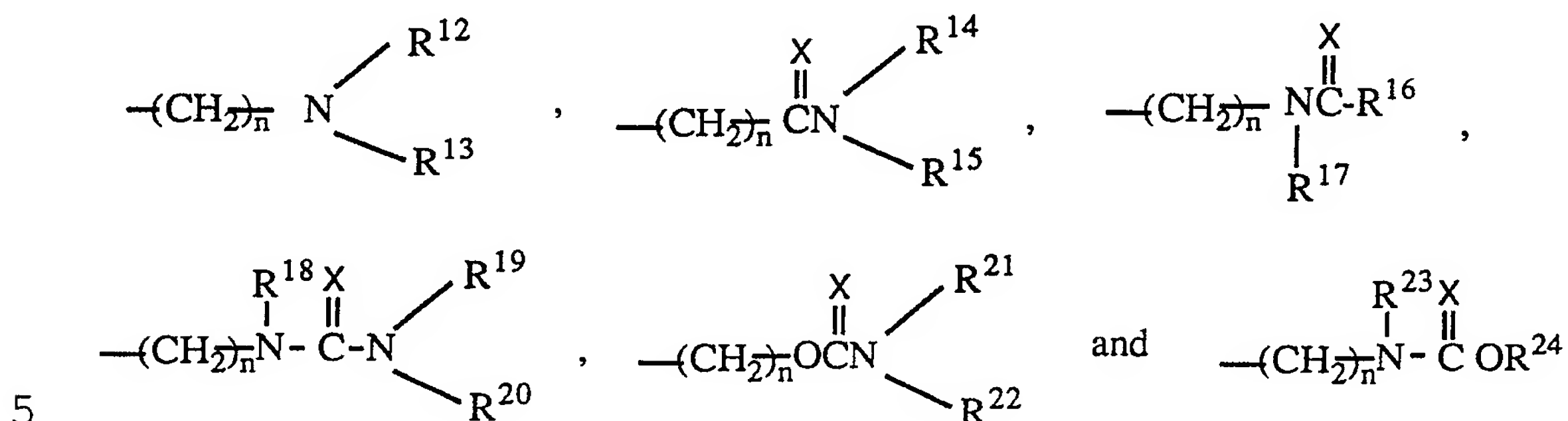
15

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

87. The method of Claim 86 wherein m is one;
- 20 wherein each of R<sup>0</sup> through R<sup>11</sup> is independently selected from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, mercaptocarbonyl, alkoxycarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, alkylthio, cycloalkylthio, arylthio, aralkylthio,
- 25 aralkylthiocarbonylthio, mercapto, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, phthalimido, phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and cycloheteroalkylcarbonylalkyl
- 30 wherein each of said heteroaryl- and cycloheteroalkyl-containing groups has one or more hetero ring atoms
- 35

**SUBSTITUTE SHEET**

selected from oxygen, sulfur and nitrogen atoms, and wherein each of R<sup>0</sup> through R<sup>11</sup> may be further independently selected from amino and amido radicals of the formula



wherein X is selected from oxygen atom or sulfur atom;

10 wherein each n is a number independently selected from zero  
to six, inclusive;

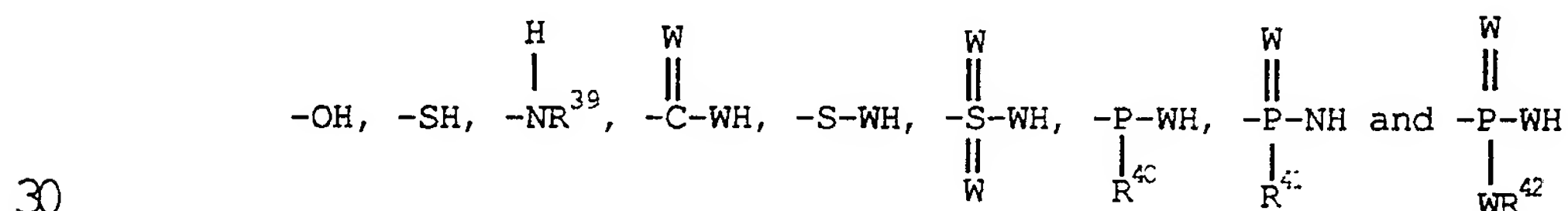
wherein each of R<sup>12</sup> through R<sup>24</sup> is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl;

and herein each of R<sup>3</sup> through R<sup>11</sup> may be an acidic moiety further independently selected from hydrido and haloalkyl, and from acidic moieties of the formula

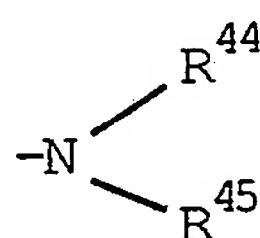


wherein n is a number selected from zero through three,  
25 inclusive;

wherein A is selected from carboxylic acid and bioisosteres of carboxylic acid selected from



wherein each W is independently selected from oxygen atom, sulfur atom and NR<sup>43</sup>; wherein each of R<sup>39</sup>, R<sup>40</sup>, R<sup>41</sup>, R<sup>42</sup> and R<sup>43</sup> is independently selected from hydrido, alkyl, haloalkyl, haloalkylsulfonyl, haloalkylcarbonyl, cycloalkyl, cycloalkylalkyl, aryl and aralkyl; wherein each of R<sup>39</sup>, R<sup>40</sup>, R<sup>41</sup> and R<sup>42</sup> may be further independently selected from amino radicals of the formula



10

wherein each of R<sup>44</sup> and R<sup>45</sup> is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl, and wherein R<sup>44</sup> and R<sup>45</sup> taken together may form a heterocyclic group having five to seven ring members including the nitrogen atom of said amino radical, which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms and which heterocyclic group may be saturated or partially unsaturated; wherein R<sup>44</sup> and R<sup>45</sup> taken together may form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino radical and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms; wherein each of R<sup>40</sup> and R<sup>41</sup> may be further independently selected from hydroxy, alkoxy, alkylthio, aryloxy, arylthio, aralkylthio and aralkoxy; and the amide, ester and salt derivatives of said acidic groups;

30

wherein said bioisostere of carboxylic acid may be further selected from heterocyclic acidic groups consisting of heterocyclic rings of four to about nine ring members, which heterocyclic ring contains at least one hetero atom selected from oxygen, sulfur and nitrogen atoms, which

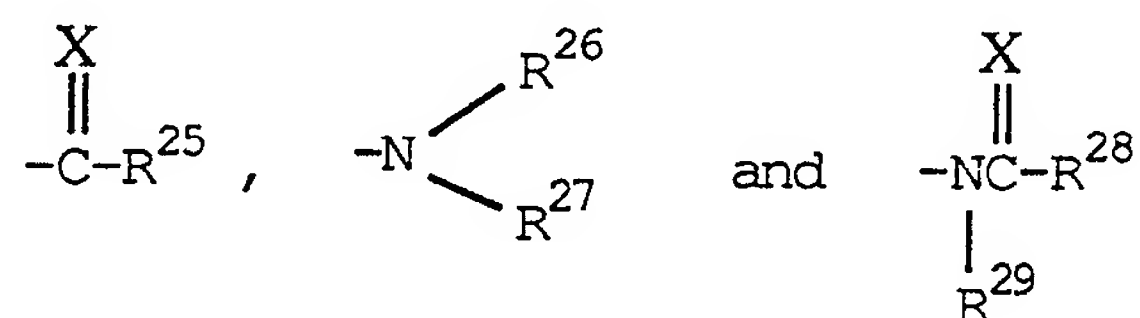
35



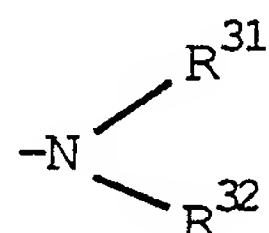
heterocyclic ring may be saturated, fully unsaturated or partially unsaturated, and which heterocyclic ring may be attached at a single position selected from  $R^3$  through  $R^{11}$  or may be attached at any two adjacent positions selected from  $R^3$  through  $R^{11}$  so as to form a fused-ring system with one of the phenyl rings of the biphenyl moiety of Formula I; and the amide, ester and salt derivatives of said heterocyclic acidic groups;

wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, aryl and aralkyl;

and wherein any of the foregoing  $R^1$  through  $R^{24}$ , Y and A groups having a substitutable position may be substituted by one or more groups selected from alkyl, difluoroalkyl, alkenyl, aralkyl, hydroxyalkyl, trifluoromethyl, alkoxy, aryloxy, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxy carbonyl, carboxyl, mercaptocarbonyl, alkylthio, alkylthiocarbonyl, and amino and amido radicals of the formula



wherein X is selected from oxygen atom and sulfur atom; wherein  $R^{25}$  is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl and  $\text{DR}^{30}$  and



wherein D is selected from oxygen atom and sulfur atom, wherein  $R^{30}$  is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl and aryl;

**SUBSTITUTE SHEET**

wherein each of R<sup>26</sup>, R<sup>27</sup>, R<sup>28</sup>, R<sup>29</sup>, R<sup>31</sup> and R<sup>32</sup> is  
independently selected from hydrido, alkyl, cycloalkyl,  
cyano, hydroxyalkyl, haloalkyl, cycloalkylalkyl,  
5 alkoxyalkyl, alkanoyl, alkoxycarbonyl, carboxyl,  
haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl;

with the proviso that at least one of said R<sup>1</sup> through R<sup>24</sup>,  
Y and A substituents contains a terminal primary or  
10 secondary amino moiety or a moiety convertible to a primary  
or secondary amino moiety;

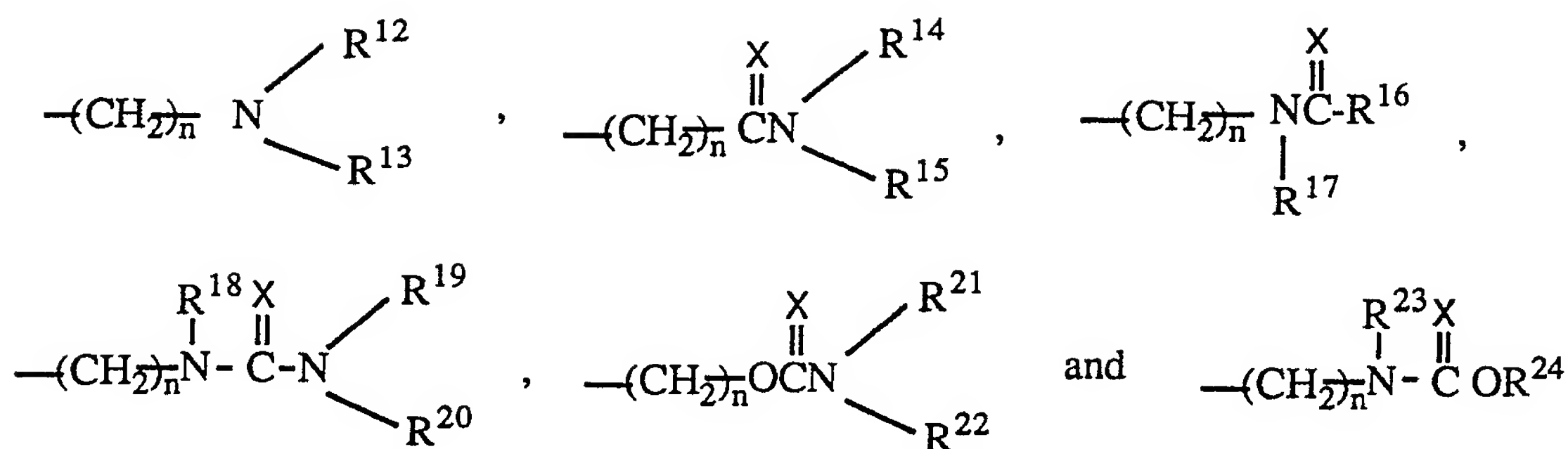
or a tautomer thereof or a pharmaceutically-acceptable salt  
thereof.

15

88. The method of Claim 87 wherein m is one;  
wherein each of R<sup>0</sup>, R<sup>1</sup> and R<sup>2</sup> is independently selected  
from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl,  
cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl, aryloxy,  
20 aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl,  
alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl,  
cycloalkynyl, cyano, nitro, carboxyl, carboxyalkyl,  
alkylcarbonyloxy, alkylcarbonyloxyalkyl,  
alkoxycarbonylalkyl, aralkoxycarbonylalkyl,  
25 aralkylcarbonyloxyalkyl, mercaptocarbonyl, mercaptoalkyl,  
alkoxycarbonyloxy, alkylthio, cycloalkylthio, arylthio,  
aralkylthio, mercapto, alkylsulfinyl, alkylsulfonyl,  
aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl,  
arylsulfonyl, phthalimido, phthalimidoalkyl, heteroaryl,  
30 heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl  
and cycloheteroalkylcarbonylalkyl wherein each of said  
heteroaryl- and cycloheteroalkyl-containing groups has one  
or more hetero ring atoms selected from oxygen, sulfur and  
nitrogen atoms, and wherein each of R<sup>0</sup> through R<sup>11</sup> may be  
35 further independently selected from amino and amido  
radicals of the formula



357



wherein X is selected from oxygen atom and sulfur atom;

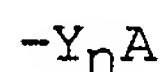
5

wherein each n is a number independently selected from zero to six, inclusive;

10 wherein each of R<sup>12</sup> through R<sup>24</sup> is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl;

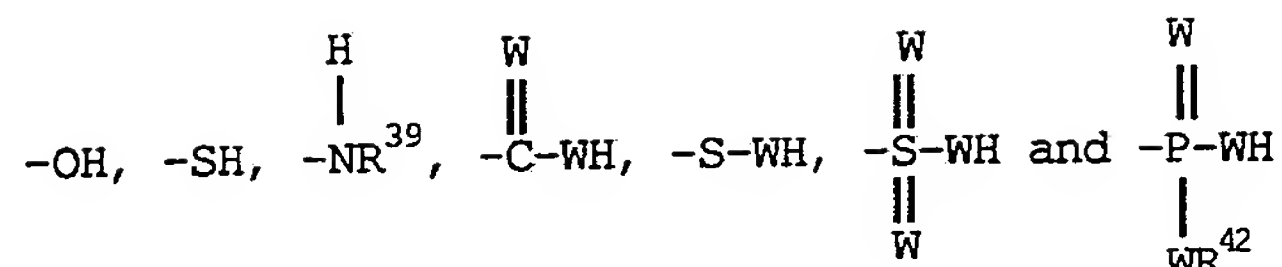
15 wherein each of R<sup>3</sup> through R<sup>11</sup> is independently selected from hydrido, hydroxy, alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxy carbonyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, cyano, nitro, carboxyl, alkylthio, 20 aralkylthio, mercapto, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms;

25 and wherein each of R<sup>3</sup> through R<sup>11</sup> may be an acidic moiety further independently selected from acidic moieties of the formula

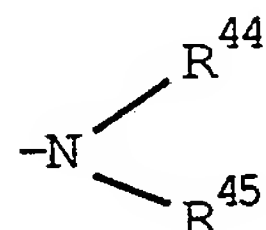


30 wherein n is a number selected from zero through three, inclusive; wherein A is selected from carboxylic acid and bioisosteres of carboxylic acid selected from

358



wherein each W is independently selected from oxygen atom,  
 5 sulfur atom and  $\text{NR}^{43}$ ; wherein each of  $\text{R}^{39}$ ,  $\text{R}^{42}$  and  $\text{R}^{43}$  is  
 independently selected from hydrido, alkyl, haloalkyl,  
 haloalkylsulfonyl, haloalkylcarbonyl, cycloalkyl,  
 cycloalkylalkyl, aryl and aralkyl; wherein each of  $\text{R}^{39}$  and  
 10  $\text{R}^{42}$  may be further independently selected from amino  
 radical of the formula



wherein each of  $\text{R}^{44}$  and  $\text{R}^{45}$  is independently selected from  
 15 hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl,  
 cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl, and wherein  
 $\text{R}^{44}$  and  $\text{R}^{45}$  taken together may form a heterocyclic group  
 having five to seven ring members including the nitrogen  
 atom of said amino radical, which heterocyclic group may  
 20 further contain one or more hetero atoms as ring members  
 selected from oxygen, nitrogen and sulfur atoms, and which  
 heterocyclic group may be saturated or partially  
 unsaturated; wherein  $\text{R}^{44}$  and  $\text{R}^{45}$  taken together may form an  
 aromatic heterocyclic group having five ring members  
 25 including the nitrogen atom of said amino radical and which  
 aromatic heterocyclic group may further contain one or more  
 hetero atoms as ring atoms selected from oxygen, nitrogen  
 and sulfur atoms; and the amide, ester and salt derivatives  
 of said acidic groups; wherein said bioisostere of  
 30 carboxylic acid may be further selected from heterocyclic  
 acidic groups consisting of heterocyclic rings of four to  
 about nine ring members, which ring contains at least one  
 hetero atom, selected from oxygen, sulfur and nitrogen  
 atoms, which heterocyclic ring may be saturated, fully  
 35 unsaturated or partially unsaturated, and which

**SUBSTITUTE SHEET**

heterocyclic ring may be attached at a single position selected from  $R^3$  through  $R^{11}$  or may be attached at any two adjacent positions selected from  $R^3$  through  $R^{11}$  so as to form a fused-ring system with one of the phenyl rings of Formula I; and the amide, ester and salt derivatives of said heterocyclic acidic groups;

wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, aryl and aralkyl;

wherein each of  $R^1$  through  $R^{24}$ , Y and A independently may be substituted at any substitutable position with one or more groups selected from alkyl, cycloalkyl, cycloalkylalkyl, hydroxy, oxo, trifluoromethyl, difluoroalkyl, alkoxycarbonyl, cyano, nitro, alkylsulfonyl, haloalkylsulfonyl, aryl, aralkyl, alkoxy, aryloxy and aralkoxy;

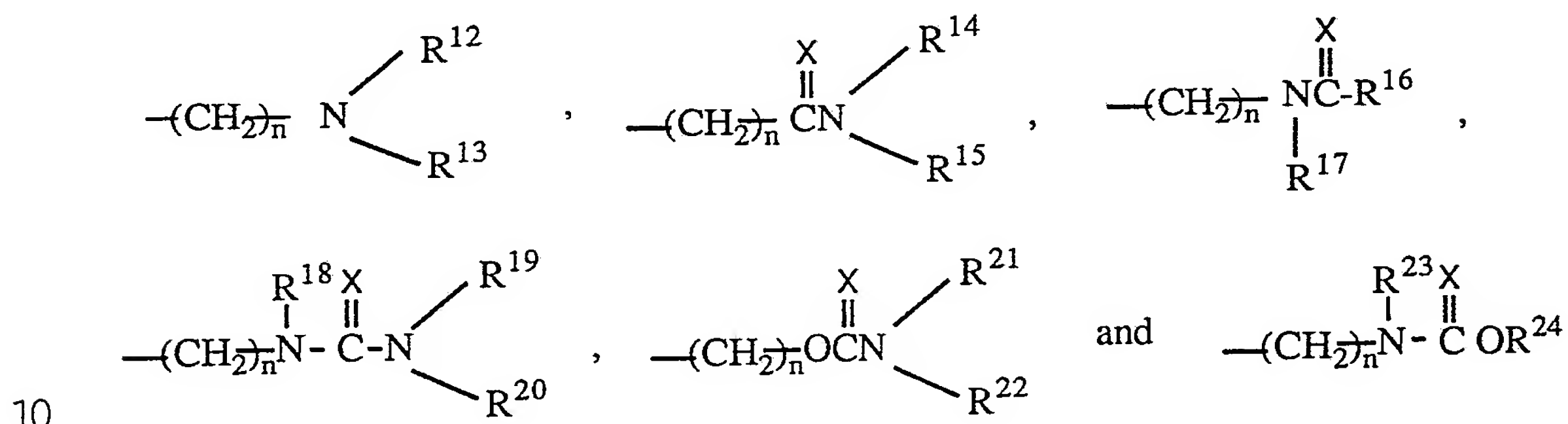
with the proviso that at least one of said  $R^1$  through  $R^{24}$ , Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

89. The method of Claim 88 wherein m is one; wherein each of  $R^0$ ,  $R^1$  and  $R^2$  is independently selected from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, benzoyl, phenoxy, phenoxyalkyl, phenalkyloxy, phenylthio, phenalkylthio, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cycloalkyl, alkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, mercaptocarbonyl, mercaptoalkyl, alkoxycarbonyloxy, alkylthio, cycloalkylthio, phthalimido,

**SUBSTITUTE SHEET**

phthalimidoalkyl, heteroaryl, heteroarylalkyl,  
 cycloheteroalkyl, cycloheteroalkylalkyl and  
 cycloheteroalkylcarbonylalkyl wherein each of said  
 heteroaryl- and cycloheteroalkyl-containing groups has one  
 5 or more hetero ring atoms selected from oxygen, sulfur and  
 nitrogen atoms, and wherein each of  $R^0$  through  $R^{11}$  may be  
 further independently selected from amino and amido  
 radicals of the formula



wherein X is selected from oxygen atom and sulfur atom;

15 wherein each n is a number independently selected from zero  
 to six, inclusive;

wherein each of  $R^{12}$  through  $R^{24}$  is independently selected  
 from hydrido, alkyl, cycloalkyl, cyano, amino,  
 20 hydroxyalkyl, alkoxyalkyl, phenalkyl and phenyl;

wherein each of  $R^3$  through  $R^{11}$  is independently selected  
 from hydrido, hydroxy, alkyl, hydroxyalkyl, halo,  
 haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, phenalkyl,  
 25 phenyl, benzoyl, phenoxy, phenalkyloxy, alkoxyalkyl,  
 alkylcarbonyl, alkoxycarbonyl, alkenyl, cyano, nitro,  
 carboxyl, alkylthio, mercapto and heteroaryl having one or  
 more ring atoms selected from oxygen, sulfur and nitrogen  
 atoms;

30

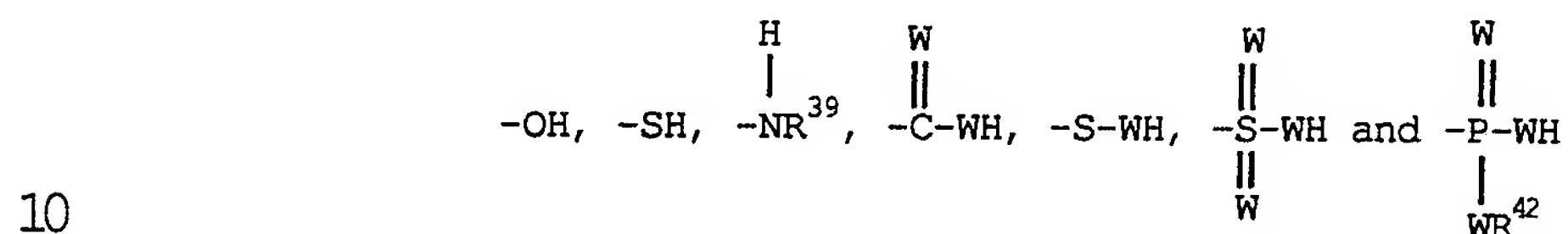
361

and wherein each of  $R^3$  through  $R^{11}$  may be an acidic moiety further independently selected from acidic moieties of the formula



5

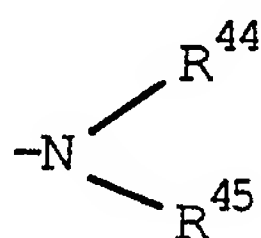
wherein  $n$  is a number selected from zero through two, inclusive; wherein  $A$  is selected from carboxylic acid and bioisosteres of carboxylic acid selected from



10

wherein each  $W$  is independently selected from oxygen atom, sulfur atom and  $NR^{43}$ ; wherein each of  $R^{39}$ ,  $R^{42}$  and  $R^{43}$  is independently selected from hydrido, alkyl, haloalkyl, haloalkylsulfonyl, haloalkylcarbonyl, cycloalkyl, phenyl and benzyl; wherein each of  $R^{39}$  and  $R^{42}$  may be further independently selected from amino radical of the formula

15



20

wherein each of  $R^{44}$  and  $R^{45}$  is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, alkoxyalkyl, benzyl and phenyl; and the amide, ester and salt derivatives of said acidic groups;

25

wherein said bioisostere of carboxylic acid may be further selected from heterocyclic acidic groups consisting of heterocyclic rings of four to about nine ring members, which ring contains at least one hetero atom, selected from oxygen, sulfur and nitrogen atoms, which heterocyclic ring may be saturated, fully unsaturated or partially unsaturated, and which heterocyclic ring may be attached at a single position selected from  $R^3$  through  $R^{11}$  or may be attached at any two adjacent positions selected from  $R^3$  through  $R^{11}$  so as to form a fused-ring system with one of

30

35

the phenyl rings of the biphenyl moiety of Formula I; and the amide, ester and salt derivatives of said heterocyclic acidic groups;

- 5 wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, phenyl, phenalkyl and aralkyl;

- 10 wherein each of  $R^1$  through  $R^{24}$ , Y and A and independently may be substituted at any substitutable position with one or more groups selected from alkyl, cycloalkyl, cycloalkylalkyl, hydroxy, oxo, trifluoromethyl, difluoroalkyl, alkoxy carbonyl, cyano, nitro, alkylsulfonyl, haloalkylsulfonyl, aryl, aralkyl, alkoxy, aryloxy and  
15 aralkoxy;

- with the proviso that at least one of said  $R^1$  through  $R^{24}$ , Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary  
20 or secondary amino moiety;

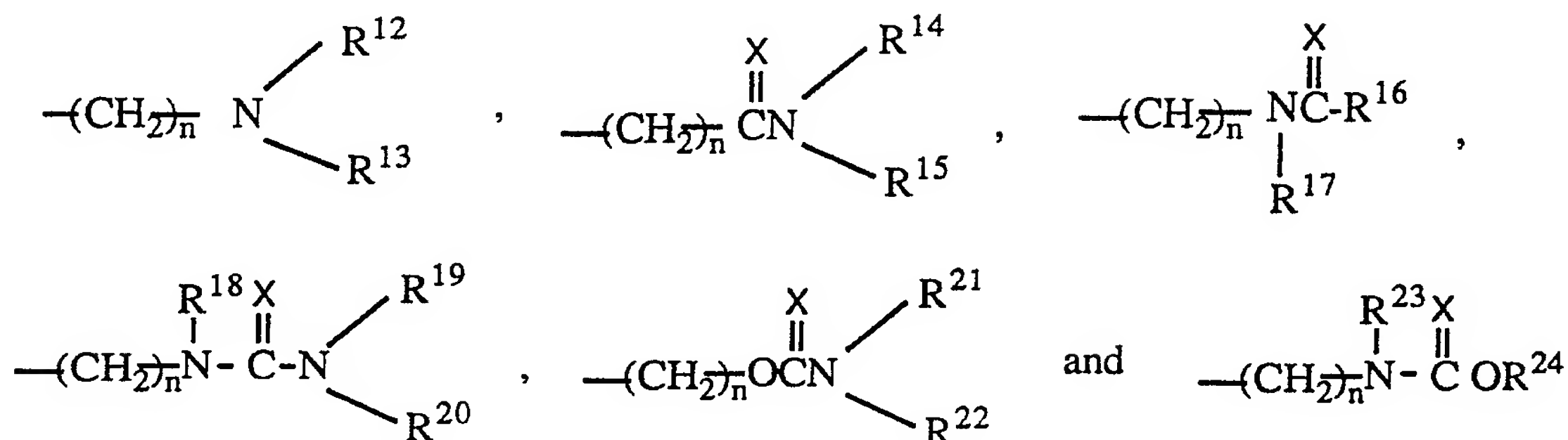
or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

- 25 90. The method of Claim 89 wherein m is one; wherein  $R^0$  is selected from alkyl, alkenyl, phenyl, alkylthio, cycloalkyl, cycloalkylalkyl and cycloalkylthio; wherein each of  $R^1$  and  $R^2$  is independently selected from  
30 alkyl, aminoalkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, benzoyl, phenoxy, phenoxyalkyl, phenalkyloxy, phenylthio, phenalkylthio, aralkoxy, alkoxyalkyl, acetyl, alkoxy carbonyl, alkenyl, cycloalkenyl, alkynyl, cyano,  
35 nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, mercaptoalkyl, mercaptocarbonyl, alkoxy carbonyloxy, alkylcarbonyloxyalkyl, alkoxy carbonylalkyl, aralkoxy carbonylalkyl, aralkylcarbonyloxyalkyl, phthalimido, phthalimidoalkyl, imidazoalkyl, tetrazole,



363

tetrazolealkyl, alkylthio, cycloalkylthio, and amino and amido radicals of the formula



5

wherein X is selected from oxygen atom and sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

10

wherein each of R<sup>12</sup> through R<sup>24</sup> is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, hydroxyalkyl, alkoxyalkyl, phenalkyl and phenyl;

15

wherein each of R<sup>3</sup> through R<sup>11</sup> is independently selected from hydrido, hydroxy, alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, phenalkyl, phenyl, benzoyl, phenoxy, phenalkyloxy, alkoxyalkyl, acetyl, alkoxycarbonyl, alkenyl, cyano, nitro, carboxyl, alkylthio and mercapto;

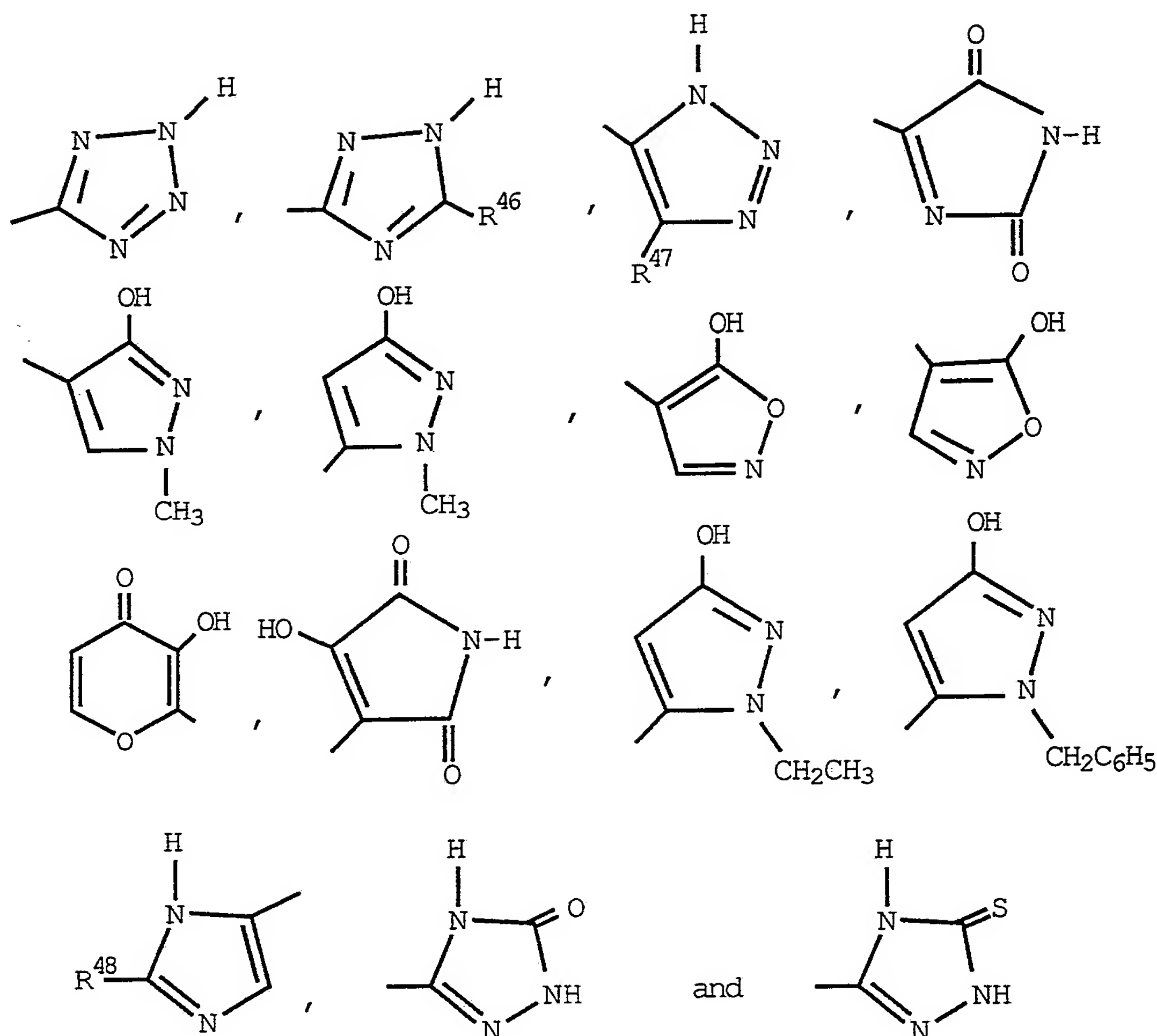
20

and wherein each of R<sup>3</sup> through R<sup>11</sup> may be an acidic moiety further independently selected from acidic moieties consisting of CO<sub>2</sub>H, CO<sub>2</sub>CH<sub>3</sub>, SH, CH<sub>2</sub>SH, C<sub>2</sub>H<sub>4</sub>SH, PO<sub>3</sub>H<sub>2</sub>,

25

NHSO<sub>2</sub>CF<sub>3</sub>, NHSO<sub>2</sub>C<sub>6</sub>F<sub>5</sub>, SO<sub>3</sub>H, CONHNH<sub>2</sub>, CONHNHSO<sub>2</sub>CF<sub>3</sub>, CONHOCH<sub>3</sub>, CONHOC<sub>2</sub>H<sub>5</sub>, CONHCF<sub>3</sub>, OH, CH<sub>2</sub>OH, C<sub>2</sub>H<sub>4</sub>OH, OPO<sub>3</sub>H<sub>2</sub>, OSO<sub>3</sub>H,

364

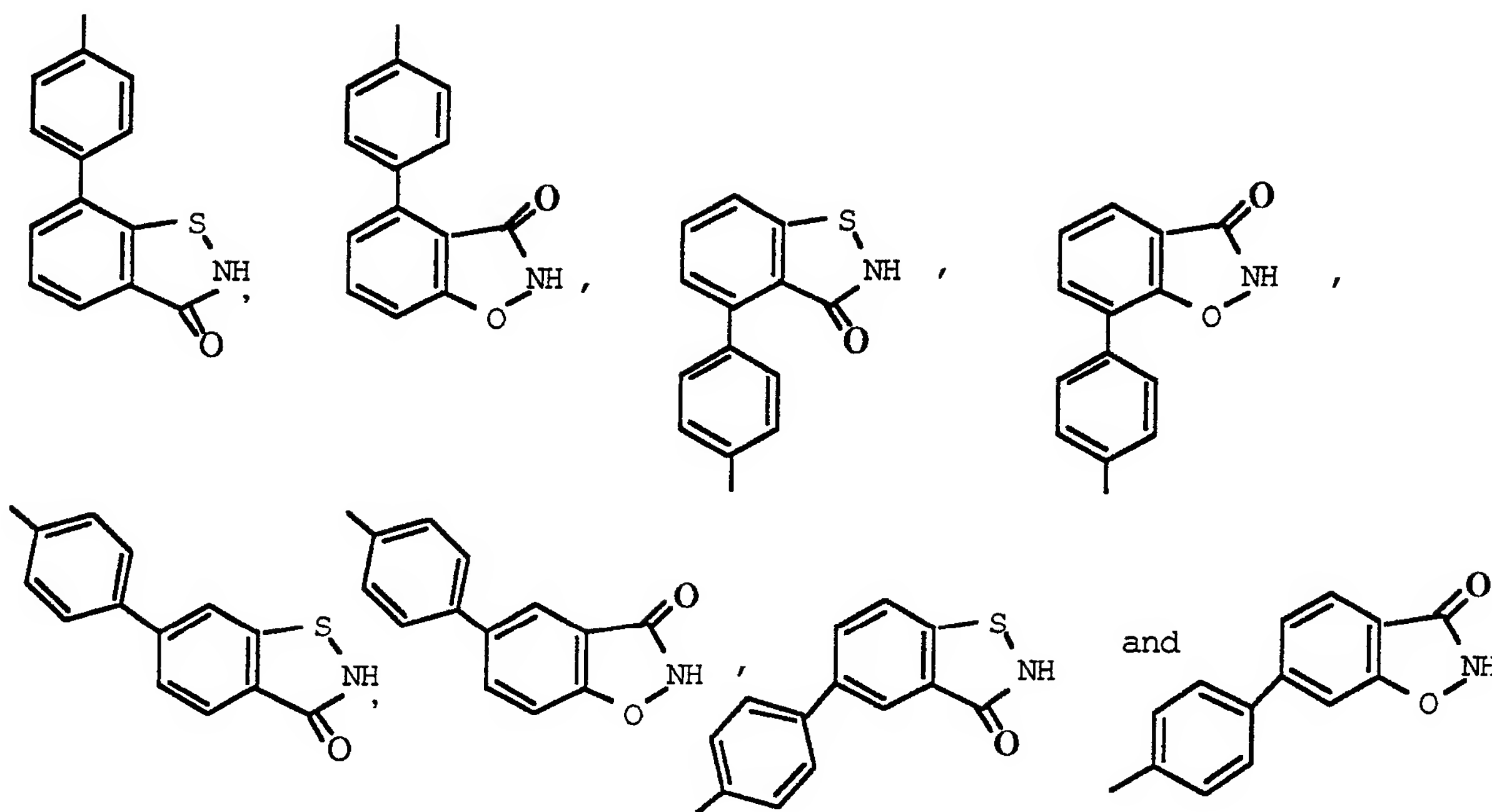


wherein each of R<sup>46</sup>, R<sup>47</sup> and R<sup>48</sup> is independently selected  
 5 from H, Cl, CN, NO<sub>2</sub>, CF<sub>3</sub>, C<sub>2</sub>F<sub>5</sub>, C<sub>3</sub>F<sub>7</sub>, CHF<sub>2</sub>, CH<sub>2</sub>F, CO<sub>2</sub>CH<sub>3</sub>,  
 CO<sub>2</sub>C<sub>2</sub>H<sub>5</sub>, SO<sub>2</sub>CH<sub>3</sub>, SO<sub>2</sub>CF<sub>3</sub> and SO<sub>2</sub>C<sub>6</sub>F<sub>5</sub>; wherein Z is selected  
 from O, S, NR<sup>49</sup> and CH<sub>2</sub>; wherein R<sup>49</sup> is selected from  
 hydrido, CH<sub>3</sub> and CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>; and wherein said acidic moiety  
 10 may be a heterocyclic acidic group attached at any two  
 adjacent positions of R<sup>3</sup> through R<sup>11</sup> so as to form a fused  
 ring system so as to include one of the phenyl rings of the  
 biphenyl moiety of Formula I, said biphenyl fused ring  
 system selected from

**SUBSTITUTE SHEET**



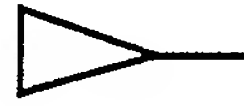


365



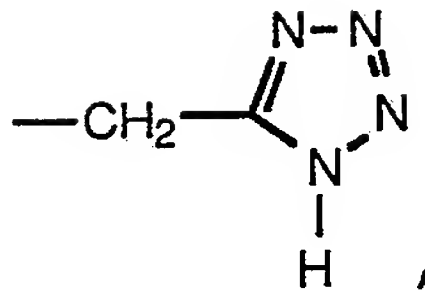



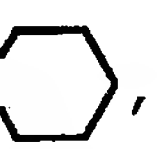
and the esters, amides and salts of said acidic moieties;

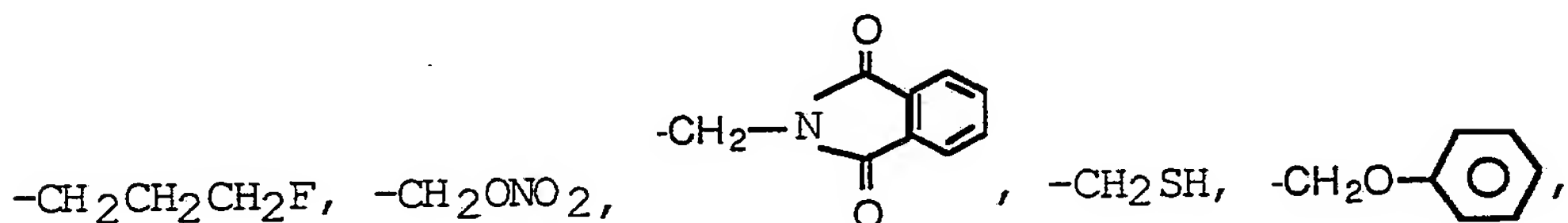
- 5 with the proviso that at least one of said  $R^1$  through  $R^{24}$  substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;
- 10 or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

91. The method of Claim 90 wherein m is one; wherein  $R^0$  is selected from  $C_4H_9(n)$ ,  $CH_3CH_2CH=CH$ ,  $C_3H_7(N)$ ,  
 15  $SC_3H_7$ , , ,  $C_2H_5$ ,  $C_5H_{11}(n)$ ,  $C_6H_{13}(n)$ ,  
 $SC_4H_9$ , ,  $CH_3CH=CH$  and  $CH_3CH_2CH_2CH=CH-$ ; wherein each of  $R^1$  and  $R^2$  is independently selected from amino, aminomethyl, aminoethyl, aminopropyl,  $CH_2OH$ ,  $CH_2OCOCH_3$ ,  $CH_2Cl$ ,  $Cl$ ,  $CH_2OCH_3$ ,  $CH_2OCH(CH_3)_2$ ,  $I$ ,  $CHO$ ,

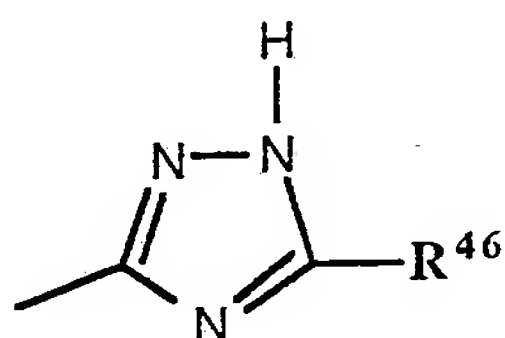
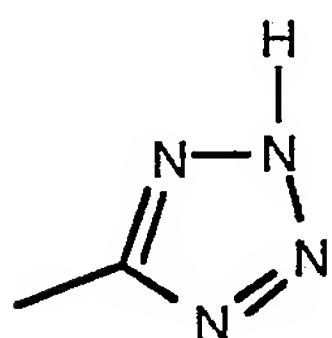
SUBSTITUTE SHEET

366

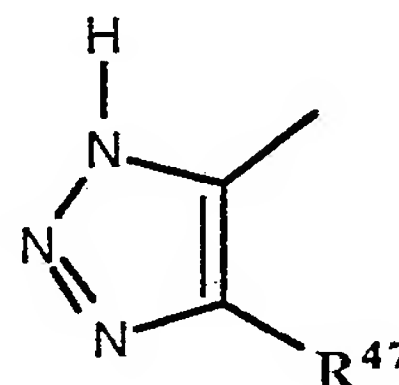
- CH<sub>2</sub>CO<sub>2</sub>H, CH(CH<sub>3</sub>)CO<sub>2</sub>H, NO<sub>2</sub>, Cl,
- 
- CH<sub>2</sub>OCOCH<sub>2</sub>CH<sub>2</sub>-, -CO<sub>2</sub>CH<sub>3</sub>, -CONH<sub>2</sub>, -CONHCH<sub>3</sub>, CON(CH<sub>3</sub>)<sub>2</sub>,
- CH<sub>2</sub>-NHCO<sub>2</sub>C<sub>2</sub>H<sub>5</sub>, -CH<sub>2</sub>NHCO<sub>2</sub>-, -CH<sub>2</sub>NHCO<sub>2</sub>CH<sub>3</sub>, -
- CH<sub>2</sub>NHCO<sub>2</sub>C<sub>3</sub>H<sub>7</sub>,
- 5 -CH<sub>2</sub>NHCO<sub>2</sub>CH<sub>2</sub>(CH<sub>3</sub>)<sub>2</sub>, -CH<sub>2</sub>NHCO<sub>2</sub>C<sub>4</sub>H<sub>9</sub>, CH<sub>2</sub>NHCO<sub>2</sub>-adamantyl,
- CH<sub>2</sub>NHCO<sub>2</sub>-(1-naphthyl), -CH<sub>2</sub>NHCONHCH<sub>3</sub>, -CH<sub>2</sub>NHCONHC<sub>2</sub>H<sub>5</sub>,
- CH<sub>2</sub>NHCONHC<sub>3</sub>H<sub>7</sub>, -CH<sub>2</sub>NHCONHC<sub>4</sub>H<sub>9</sub>, -CH<sub>2</sub>NHCONHCH(CH<sub>3</sub>)<sub>2</sub>,
- CH<sub>2</sub>NHCONH(1-naphthyl), -CH<sub>2</sub>NHCONH(1-adamantyl), CO<sub>2</sub>H,
- CH<sub>2</sub>CH<sub>2</sub>-CO-N, -CH<sub>2</sub>CH<sub>2</sub>CO-N, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CO<sub>2</sub>H,
- 10 -CH<sub>2</sub>CH<sub>2</sub>F, -CH<sub>2</sub>OCONHCH<sub>3</sub>, -CH<sub>2</sub>OCSNHCH<sub>3</sub>, -CH<sub>2</sub>NHCSOC<sub>3</sub>H<sub>7</sub>,



92. Cl, NO<sub>2</sub>, CF<sub>3</sub>, CH<sub>2</sub>OH, Br, F, I, methyl, ethyl, n-propyl,
- isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-
- pentyl, isopentyl, neopentyl, phenyl, benzyl, phenethyl,
- 15 cyclohexyl, cyclohexylmethyl, 1-oxoethyl, 1-oxopropyl, 1-
- oxobutyl, 1-oxopentyl, 1,1-dimethoxypropyl, 1,1-
- dimethoxybutyl, 1,1-dimethoxypentyl, hydroxyalkyl, halo,
- difluoromethyl, 1,1-difluoroethyl, 1,1-difluoropropyl, 1,1-
- difluorobutyl and 1,1-difluoropentyl; wherein each of R<sup>3</sup>
- 20 through 11 is hydrido, with the proviso that at least one
- of R<sup>5</sup>, R<sup>6</sup>, R<sup>8</sup> and R<sup>9</sup> is an acidic group selected from CO<sub>2</sub>H,
- SH, PO<sub>3</sub>H<sub>2</sub>, SO<sub>3</sub>H, CONHNH<sub>2</sub>, CONHNHSO<sub>2</sub>CF<sub>3</sub>, OH,



and



25






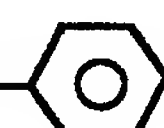
**SUBSTITUTE SHEET**

367

wherein each of  $R^{46}$  and  $R^{47}$  is independently selected from Cl, CN,  $NO_2$ ,  $CF_3$ ,  $CO_2CH_3$  and  $SO_2CF_3$ ;

5 with the proviso that at least one of said  $R^1$  through  $R^{11}$  substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

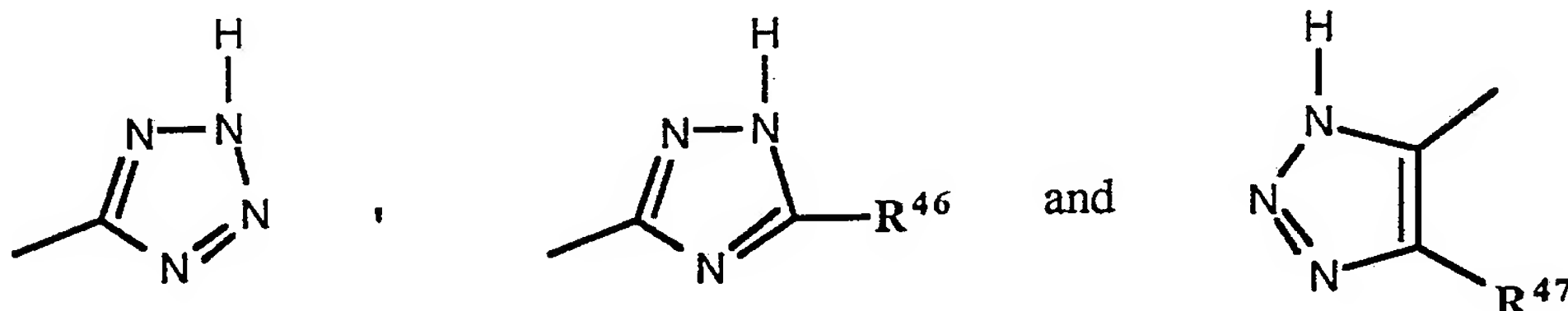
10 or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

92. The method of Claim 91 wherein m is one; wherein  $R^0$  is selected from  $C_4H_9(n)$ ,  $CH_3CH_2CH=CH$ ,  $C_3H_7(N)$ ,  $SC_3H_7$ , , ,  $C_2H_5$ ,  $C_5H_{11}(n)$ ,  $C_6H_{13}(n)$ ,   
 15  $SC_4H_9$ , ,  $CH_3CH=CH$  and  $CH_3CH_2CH_2CH=CH-$ ; wherein  $R^1$  is selected from amino, aminomethyl, aminoethyl, aminopropyl,  $CH_2OH$ ,  $CH_2OCOCH_3$ ,  $CH_2Cl$ , Cl,  $CH_2OCH_3$ ,  $CH_2OCH(CH_3)_2$ , I, CHO,  $CH_2CO_2H$ ,  $CH(CH_3)CO_2H$ ,  $-CO_2CH_3$ ,  $-CONH_2$ ,  $-CONHCH_3$ ,  $CON(CH_3)_2$ ,   
 20  $-CH_2-NHCO_2C_2H_5$ ,  $-CH_2NHCO_2-$ ,  $-CH_2NHCO_2CH_3$ ,  $-CH_2NHCO_2C_3H_7$ ,  $-CH_2NHCO_2CH_2(CH_3)_2$ ,  $-CH_2NHCO_2C_4H_9$ ,  $CH_2NHCO_2-$ adamantyl,  $-CH_2NHCO_2-(1-naphthyl)$ ,  $-CH_2NHCONHCH_3$ ,  $-CH_2NHCONHC_2H_5$ ,  $-CH_2NHCONHC_3H_7$ ,  $-CH_2NHCONHC_4H_9$ ,  $-CH_2NHCONHCH(CH_3)_2$ ,  $-CH_2NHCONH(1-naphthyl)$ ,  $-CH_2NHCONH(1-$    
 25 adamantyl),  $CO_2H$ ,  $-CH_2CH_2CO-N$ ,  $-CH_2CH_2CH_2CO_2H$ ,  $-CH_2CH_2F$ ,  $-CH_2OCONHCH_3$ ,  $-CH_2CH_2CH_2F$ ,  $-CH_2SH$  and  $-CH_2O-$ ; wherein  $R^2$  is selected from H, Cl,  $NO_2$ ,  $CF_3$ ,  $CH_2OH$ , Br, F, I, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, neopentyl,   
 30 phenyl, benzyl, phenethyl, cyclohexyl, cyclohexylmethyl, 1-oxoethyl, 1-oxopropyl, 1-oxobutyl, 1-oxopentyl, 1,1-dimethoxypropyl, 1,1-dimethoxybutyl, 1,1-dimethoxypentyl, hydroxyalkyl, halo, difluoromethyl, 1,1-difluoroethyl, 1,1-difluoropropyl, 1,1-difluorobutyl and 1,1-difluoropentyl;

SUBSTITUTE SHEET

wherein each of  $R^3$  through  $R^{11}$  is hydrido, with the proviso that at least one of  $R^5$ ,  $R^6$ ,  $R^8$  and  $R^9$  is an acidic group selected from  $CO_2H$ ,  $SH$ ,  $PO_3H_2$ ,  $SO_3H$ ,  $CONHNH_2$ ,  $CONHNHSO_2CF_3$ ,  $OH$ ,

5





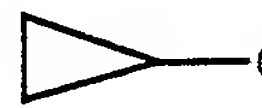
wherein each of  $R^{46}$  and  $R^{47}$  is independently selected from  $Cl$ ,  $CN$ ,  $NO_2$ ,  $CF_3$ ,  $CO_2CH_3$  and  $SO_2CF_3$ ;

10

with the proviso that at least one of said  $R^1$  through  $R^{11}$  substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;


15

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

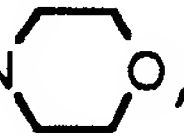
93. The method of Claim 91 wherein  $m$  is one;  
 20 wherein  $R^0$  is selected from  $C_4H_9(n)$ ,  $CH_3CH_2CH=CH$ ,  $C_3H_7(N)$ ,  $SC_3H_7$ , , ,  $C_2H_5$ ,  $C_5H_{11}(n)$ ,  $C_6H_{13}(n)$ ,  $SC_4H_9$ , ,  $CH_3CH=CH$  and  $CH_3CH_2CH_2CH=CH-$ ;  
 wherein  $R^1$  is selected from  $H$ ,  $Cl$ ,  $NO_2$ ,  $CF_3$ ,  $CH_2OH$ ,  $Br$ ,  $F$ ,  $I$ , methyl, ethyl,  $n$ -propyl, isopropyl,  $n$ -butyl, sec-butyl,  
 25 isobutyl, tert-butyl,  $n$ -pentyl, isopentyl, neopentyl, phenyl, benzyl, phenethyl, cyclohexyl, cyclohexylmethyl, 1-oxoethyl, 1-oxopropyl, 1-oxobutyl, 1-oxopentyl, 1,1-dimethoxypropyl, 1,1-dimethoxybutyl, 1,1-dimethoxypentyl, hydroxyalkyl, halo, difluoromethyl, 1,1-difluoroethyl, 1,1-difluoropropyl, 1,1-difluorobutyl and 1,1-difluoropentyl;  
 30 wherein  $R^2$  is selected from amino, aminomethyl, aminoethyl, aminopropyl,  $CH_2OH$ ,  $CH_2OCOCH_3$ ,  $CH_2Cl$ ,  $Cl$ ,  $CH_2OCH_3$ ,  $CH_2OCH(CH_3)_2$ ,  $I$ ,  $CHO$ ,


369

CH<sub>2</sub>CO<sub>2</sub>H, CH(CH<sub>3</sub>)CO<sub>2</sub>H, , -CO<sub>2</sub>CH<sub>3</sub>, -CONH<sub>2</sub>, -CONHCH<sub>3</sub>,  
CON(CH<sub>3</sub>)<sub>2</sub>,

-CH<sub>2</sub>-NHCO<sub>2</sub>C<sub>2</sub>H<sub>5</sub>, -CH<sub>2</sub>NHCO<sub>2</sub>-, -CH<sub>2</sub>NHCO<sub>2</sub>CH<sub>3</sub>, -  
CH<sub>2</sub>NHCO<sub>2</sub>C<sub>3</sub>H<sub>7</sub>,

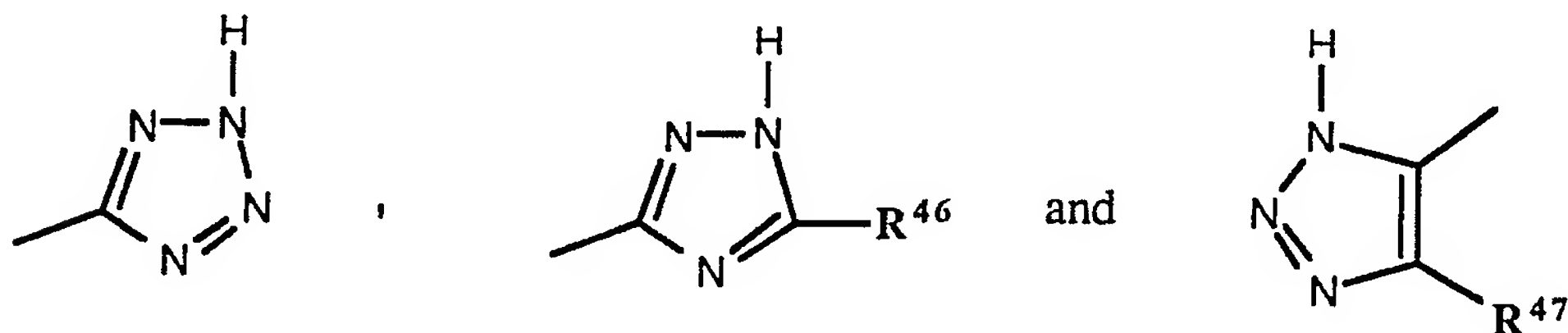
5 -CH<sub>2</sub>NHCO<sub>2</sub>CH<sub>2</sub>(CH<sub>3</sub>)<sub>2</sub>, -CH<sub>2</sub>NHCO<sub>2</sub>C<sub>4</sub>H<sub>9</sub>, CH<sub>2</sub>NHCO<sub>2</sub>-adamantyl,  
-CH<sub>2</sub>NHCO<sub>2</sub>-(1-naphthyl), -CH<sub>2</sub>NHCONHCH<sub>3</sub>, -CH<sub>2</sub>NHCONHC<sub>2</sub>H<sub>5</sub>,  
-CH<sub>2</sub>NHCONHC<sub>3</sub>H<sub>7</sub>, -CH<sub>2</sub>NHCONHC<sub>4</sub>H<sub>9</sub>, -CH<sub>2</sub>NHCONHCH(CH<sub>3</sub>)<sub>2</sub>,  
-CH<sub>2</sub>NHCONH(1-naphthyl), -CH<sub>2</sub>NHCONH(1-adamantyl), CO<sub>2</sub>H,

-CH<sub>2</sub>CH<sub>2</sub>-CO-N, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CO<sub>2</sub>H, -CH<sub>2</sub>CH<sub>2</sub>F, -CH<sub>2</sub>OCONHCH<sub>3</sub>, -

10 CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>F, -CH<sub>2</sub>SH and -CH<sub>2</sub>O-;

wherein each of R<sup>3</sup> through <sup>11</sup> is hydrido, with the proviso  
that at least one of R<sup>5</sup>, R<sup>6</sup>, R<sup>8</sup> and R<sup>9</sup> is an acidic group  
selected from CO<sub>2</sub>H, SH, PO<sub>3</sub>H<sub>2</sub>, SO<sub>3</sub>H, CONHNH<sub>2</sub>, CONHNHSO<sub>2</sub>CF<sub>3</sub>,  
OH,

15



wherein each of R<sup>46</sup> and R<sup>47</sup> is independently selected from  
Cl, CN, NO<sub>2</sub>, CF<sub>3</sub>, CO<sub>2</sub>CH<sub>3</sub> and SO<sub>2</sub>CF<sub>3</sub>;

20

with the proviso that at least one of said R<sup>1</sup> through R<sup>11</sup>  
substituents contains a terminal primary or secondary amino  
moiety or a moiety convertible to a primary or secondary  
amino moiety;

25

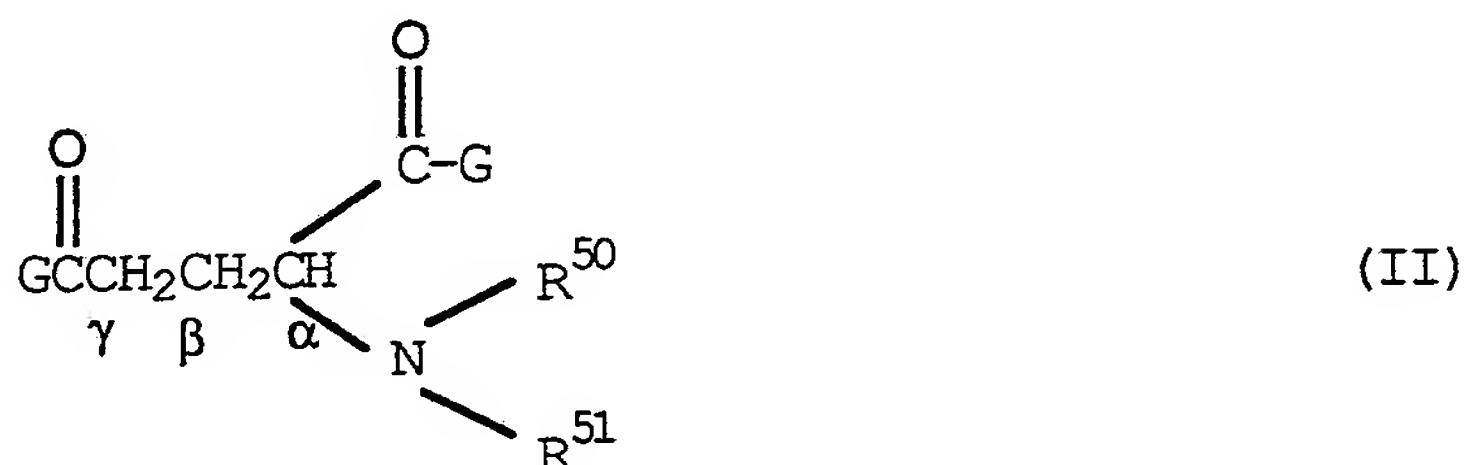
or a tautomer thereof or a pharmaceutically-acceptable salt  
thereof.

94. The method of Claim 83 wherein said second  
30 residue forms a kidney-enzyme-cleavable amide bond with the  
residue of said angiotensin II antagonist compound.

**SUBSTITUTE SHEET**

370

95. The method of Claim 94 wherein said second residue is provided by a compound of Formula II:



5 wherein each of  $\text{R}^{50}$  and  $\text{R}^{51}$  may be independently selected from hydrido, alkylcarbonyl, alkoxycarbonyl, alkoxyalkyl, hydroxyalkyl and haloalkyl; and wherein G is selected from hydroxyl, halo, mercapto,  $-\text{OR}^{52}$ ,  $-\text{SR}^{53}$  and  
 10  $-\text{NR}^{54}$  with each of  $\text{R}^{52}$ ,  $\text{R}^{53}$  and  $\text{R}^{54}$  independently selected from hydrido and alkyl; with the proviso that said Formula II compound is selected such that formation of the cleavable amide bond occurs at carbonyl moiety attached at the gamma-position carbon of said Formula II compound.

15

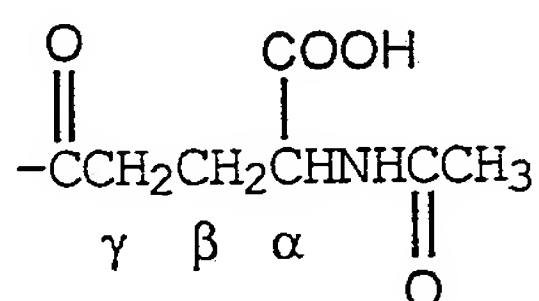
96. The method of Claim 95 wherein each G substituent is hydroxy.

20 97. The method of Claim 96 wherein each G substituent is hydroxy; wherein  $\text{R}^{50}$  is hydrido; and wherein

$\text{R}^{51}$  is selected from  $\begin{array}{c} \text{O} \\ \parallel \\ -\text{CR}^{55} \end{array}$  wherein  $\text{R}^{55}$  is selected from methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, neopentyl, n-hexyl and chloromethyl.

25

98. The method of Claim 97 wherein said second residue is



30

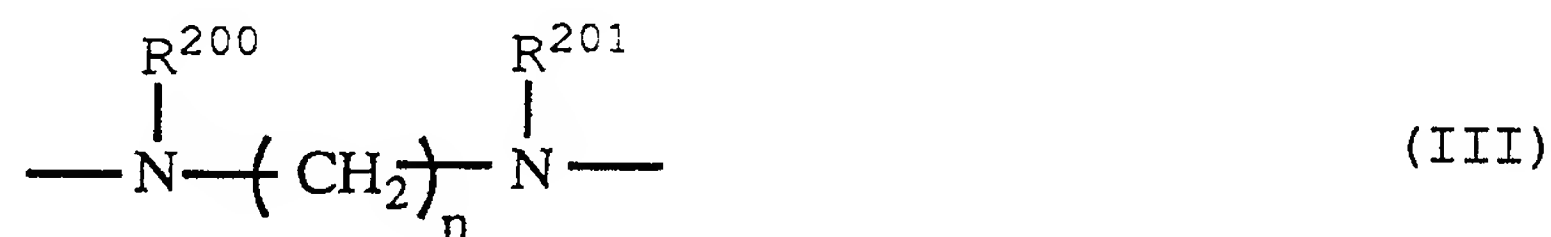
SUBSTITUTE SHEET

99. The method of Claim 83 wherein said first residue is an angiotensin II antagonist compound containing a terminal primary or secondary amino moiety selected from amino and linear or branched aminoalkyl moieties containing linear or branched alkyl groups selected from aminomethyl, aminoethyl, aminopropyl, aminoisopropyl, aminobutyl, aminosecbutyl, aminoisobutyl, aminotertbutyl, aminopentyl, aminoisopentyl and aminoneopentyl.

100. The method of Claim 83 wherein said first residue is an angiotensin II antagonist compound containing a moiety convertible to a primary or secondary amino terminal moiety.

101. The method of Claim 100 wherein said moiety convertible to an amino terminal moiety is a carboxylic acid group reactable with an amino moiety of a diamino-terminated linker group to provide a terminal amino moiety which may then be further reacted with a carboxylic acid moiety of a compound providing said second residue so as to form a hydrolyzable amide bond.

102. The method of Claim 101 wherein said diamino-terminated linker group is a divalent radical of Formula III:



wherein each of R<sup>200</sup> and R<sup>201</sup> may be independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, alkoxyalkyl, hydroxyalkyl, aralkyl, aryl, haloalkyl, amino, monoalkylamino, dialkylamino, cyanoamino, carboxyalkyl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; and wherein n is zero or a number selected from three through seven, inclusive.

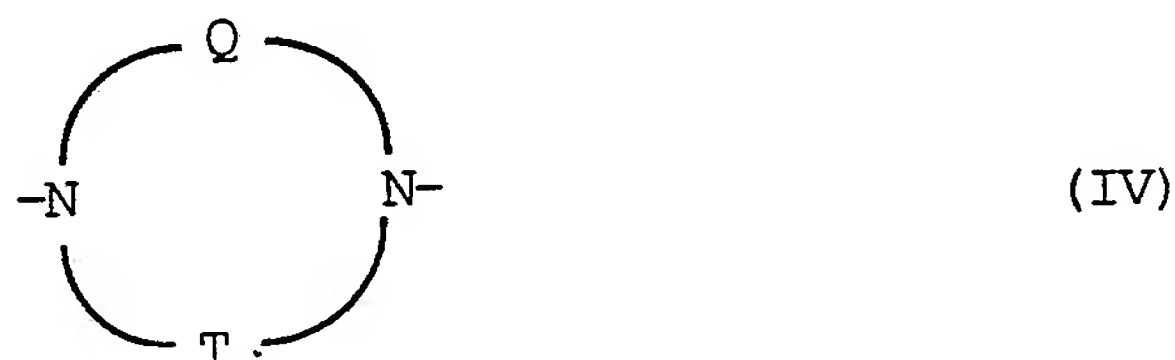
**SUBSTITUTE SHEET**



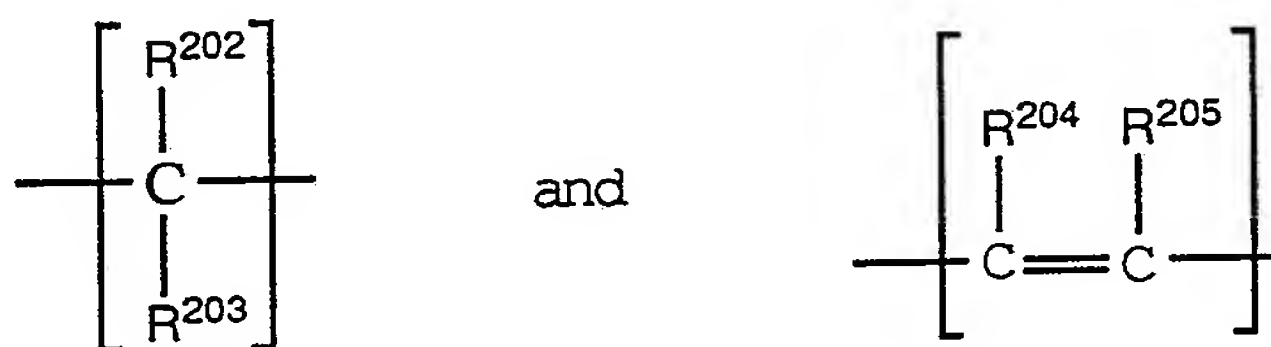
372

103. The method of Claim 102 wherein each of  $R^{200}$  and  $R^{201}$  is hydrido.

104. The method of Claim 101 wherein said  
5 diamino-terminated linker group is a divalent radical of Formula IV:



10 wherein each of Q and T is one or more groups independently selected from



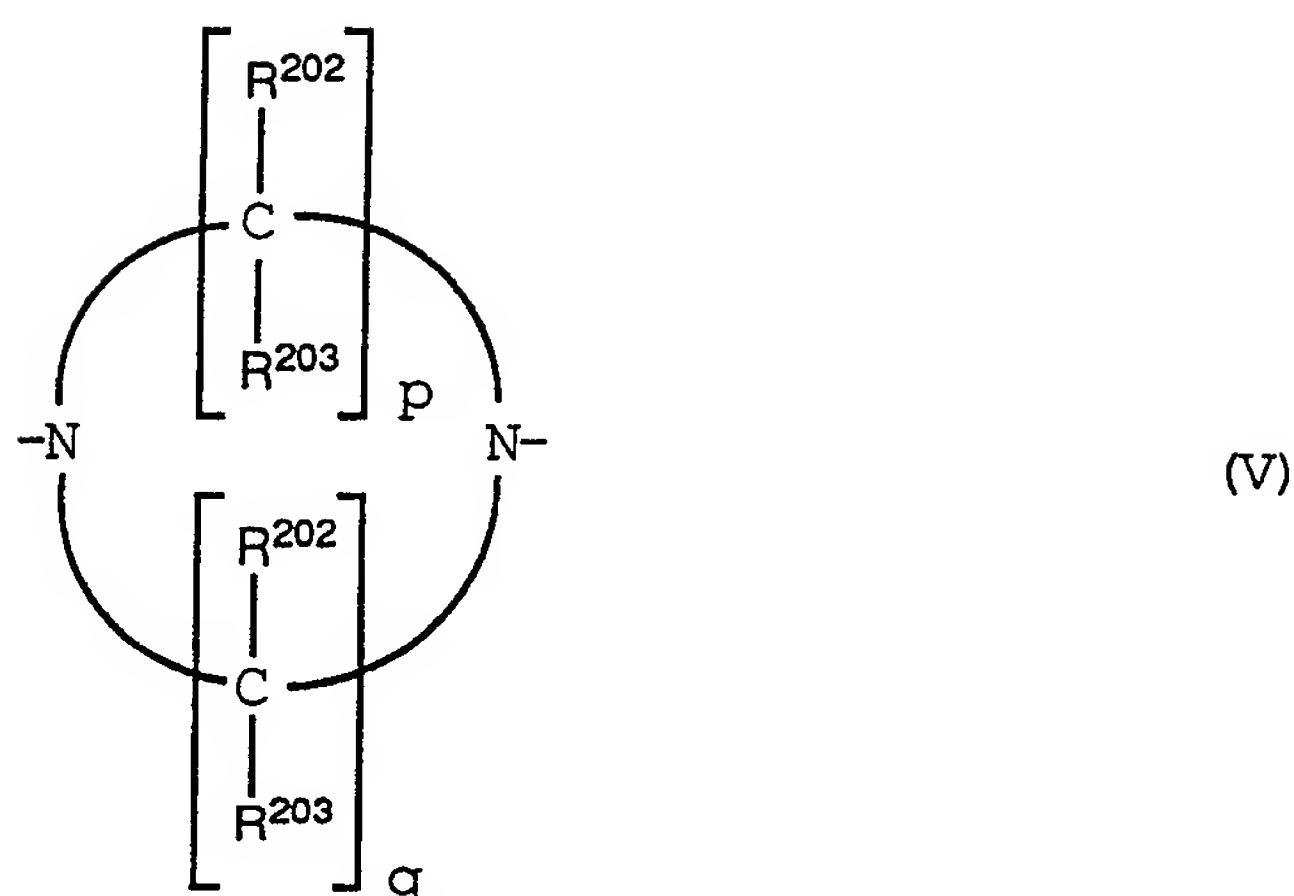
15 wherein each of  $R^{202}$  through  $R^{205}$  is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, aryloxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl,  
20 alkanoyl, alkenyl, cycloalkenyl and alkynyl.

105. The method of Claim 104 wherein said  
diamino-terminated linker group is a divalent radical of  
Formula V:

25



373



wherein each of  $R^{202}$  and  $R^{203}$  is independently selected from hydrido, hydroxy, alkyl, phenalkyl, phenyl, alkoxy, benzyloxy, phenoxy, alkoxyalkyl, hydroxyalkyl, halo, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl and alkanoyl; and wherein each of  $p$  and  $q$  is a number independently selected from one through six, inclusive; with the proviso that when each of  $R^{202}$  and  $R^{203}$  is selected from halo, hydroxy, amino, monoalkylamino and dialkylamino, then the carbon to which  $R^{202}$  or  $R^{203}$  is attached in Formula V is not adjacent to a nitrogen atom of Formula V.

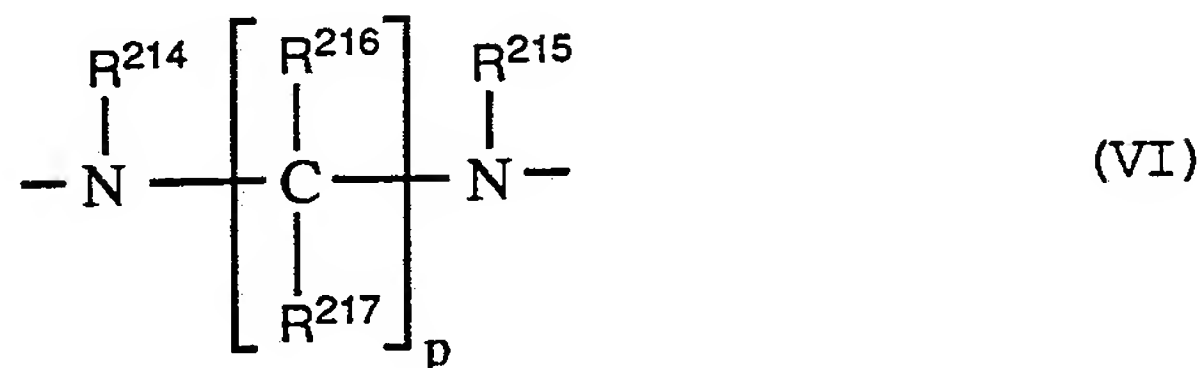
106. The method of Claim 105 wherein each of  $R^{202}$  and  $R^{203}$  is independently selected from hydrido, hydroxy, alkyl, alkoxy, amino, monoalkylamino, carboxy, carboxyalkyl and alkanoyl; and wherein each of  $p$  and  $q$  is a number independently selected from two through four, inclusive.

107. The method of Claim 106 wherein each of  $R^{202}$  and  $R^{203}$  is independently selected from hydrido, amino, monoalkylamino and carboxyl; and wherein each of  $p$  and  $q$  is independently selected from the numbers two and three.

108. The method of Claim 107 wherein each of  $R^{202}$  and  $R^{203}$  is hydrido; and wherein each of  $p$  and  $q$  is two.

109. The method of Claim 101 wherein said diamino-terminated linker group is a divalent radical of Formula VI:

5



wherein each of R<sup>214</sup> through R<sup>217</sup> is independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, hydroxyalkyl, alkoxyalkyl, aralkyl, aryl, haloalkyl, amino, 10 monoalkylamino, dialkylamino, cyanoamino, carboxyalkyl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; and wherein p is a number selected from one through six inclusive.

15

110. The method of Claim 109 wherein each of R<sup>214</sup> and R<sup>215</sup> is hydrido; wherein each of R<sup>216</sup> and R<sup>217</sup> is independently selected from hydrido, alkyl, phenalkyl, phenyl, alkoxyalkyl, hydroxyalkyl, haloalkyl and 20 carboxyalkyl; and wherein p is two or three.

25

111. The method of Claim 110 wherein each of R<sup>214</sup> and R<sup>215</sup> is hydrido; wherein each of R<sup>216</sup> and R<sup>217</sup> is independently selected from hydrido and alkyl; and wherein p is two.

112. The method of Claim 111 wherein each of R<sup>214</sup>, R<sup>215</sup>, R<sup>216</sup> and R<sup>217</sup> is hydrido; and wherein p is two.

30

113. The method of Claim 92 wherein said angiotensin II antagonist compound is 4'-[2-butyl-5-chloro-4-(hydroxymethyl)-1H-imidazol-1-ylmethyl][1,1'-biphenyl]-2-carboxylic acid.

114. The method of Claim 113 wherein said conjugate is N-acetyl-L-glutamic acid, 5-[[4'-[2-butyl-5-chloro-4-(hydroxymethyl)-1H-imidazol-1-ylmethyl][1,1'-biphenyl]-2-yl]carbonyl]hydrazide.

5

115. The method of Claim 113 wherein said conjugate is N<sup>2</sup>-acetyl-N-[[2-butyl-5-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazol-4-yl]methyl]-L-glutamine.

10

116. The method of Claim 113 which is N-acetyl-L-glutamic acid, 5-[2-butyl-5-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazol-4-yl]acetylhydrazide.

15

117. The method of Claim 93 wherein said angiotensin II antagonist compound is 4'-[2-butyl-4-chloro-5-(hydroxymethyl)-1H-imidazol-1-ylmethyl][1,1'-biphenyl]-2-carboxylic acid.

20

118. The method of Claim 117 which is N-acetyl-L-glutamic acid, 5-[[4'-[2-butyl-4-chloro-5-(hydroxymethyl)-1H-imidazol-1-ylmethyl][1,1'-biphenyl]-2-yl]carbonyl]hydrazide.

25

119. The method of Claim 117 which is N<sup>2</sup>-acetyl-N-[[2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazol-5-yl]methyl]-L-glutamine.

30

120. The method of Claim 117 which is N-acetyl-L-glutamic acid, 5-[2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazol-5-yl]acetylhydrazide.

35

121. The method of Claim 81 wherein said hypertensive-related disorder is chronic hypertension.

122. The method of Claim 81 wherein said sodium-retaining disorder is congestive heart failure.

123. The method of Claim 81 wherein said  
5 sodium-retaining disorder is cirrhosis.

124. The method of Claim 81 wherein said sodium-retaining disorder is nephrosis.

1 / 4

## Chronic Infusion of Example #81 Conjugate

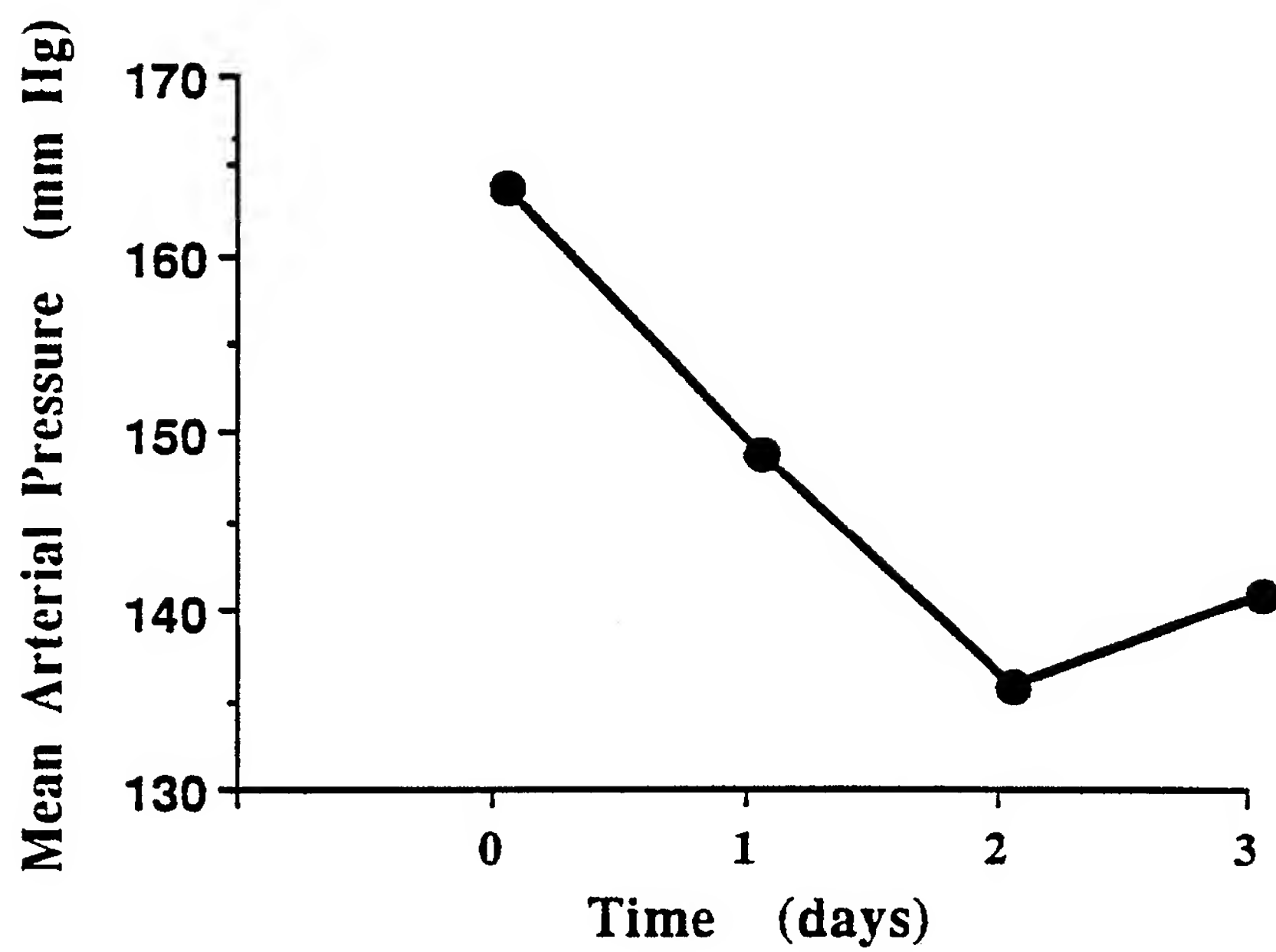
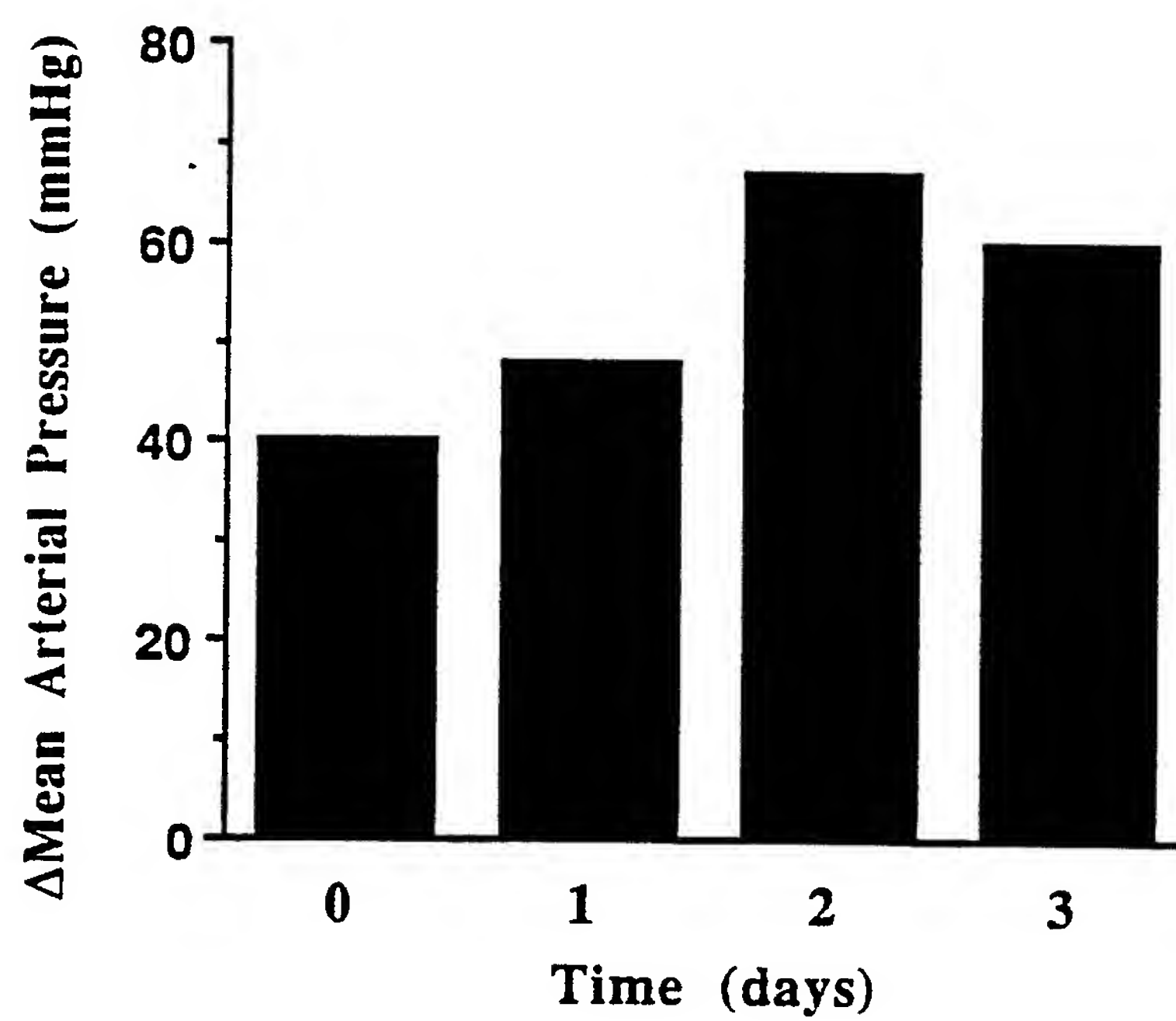


Figure 1

2/4

**Acute Angiotensin II Pressor Response During  
Chronic Infusion of Example #81 Conjugate**



**Figure 2**

3/4

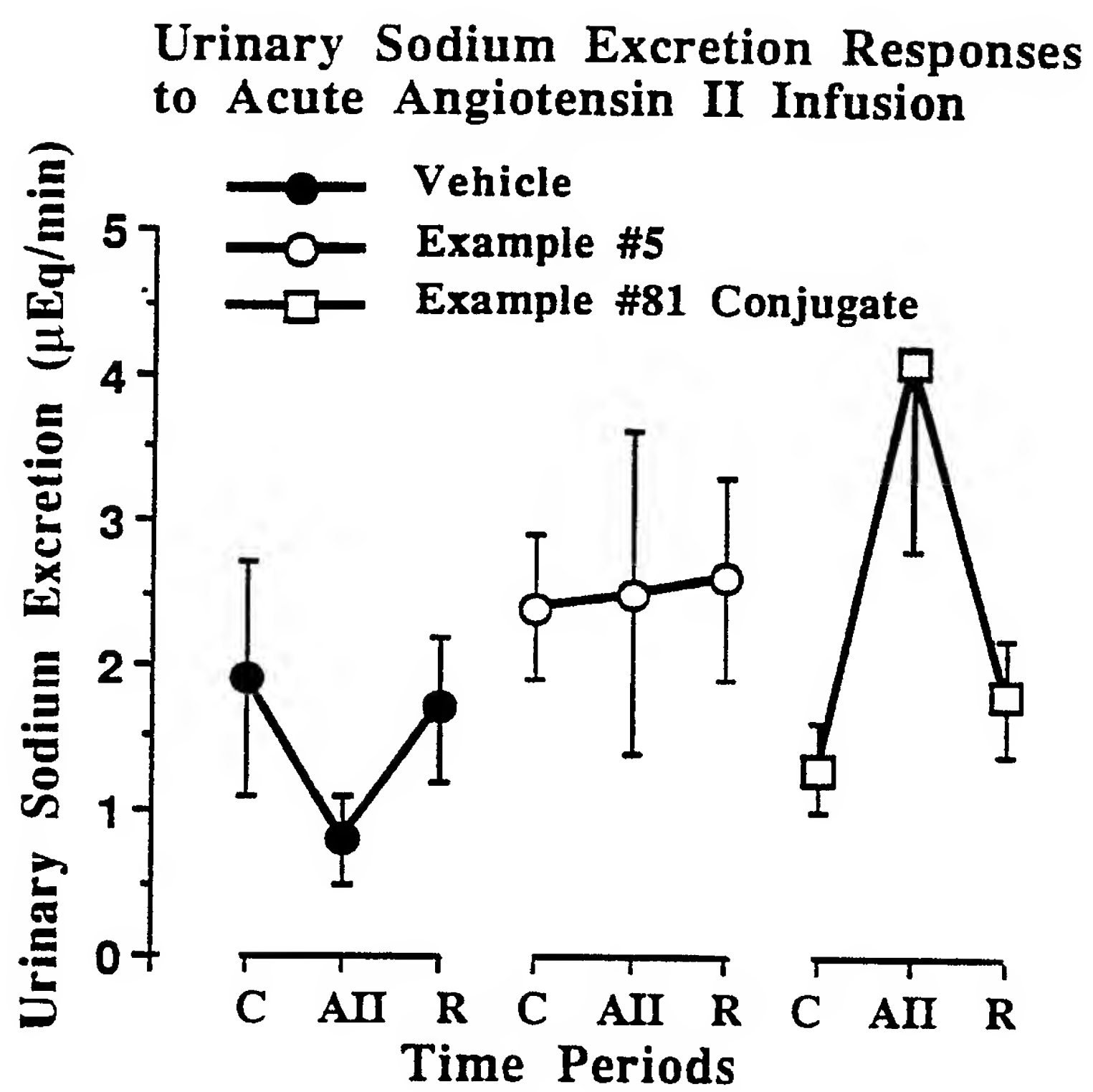
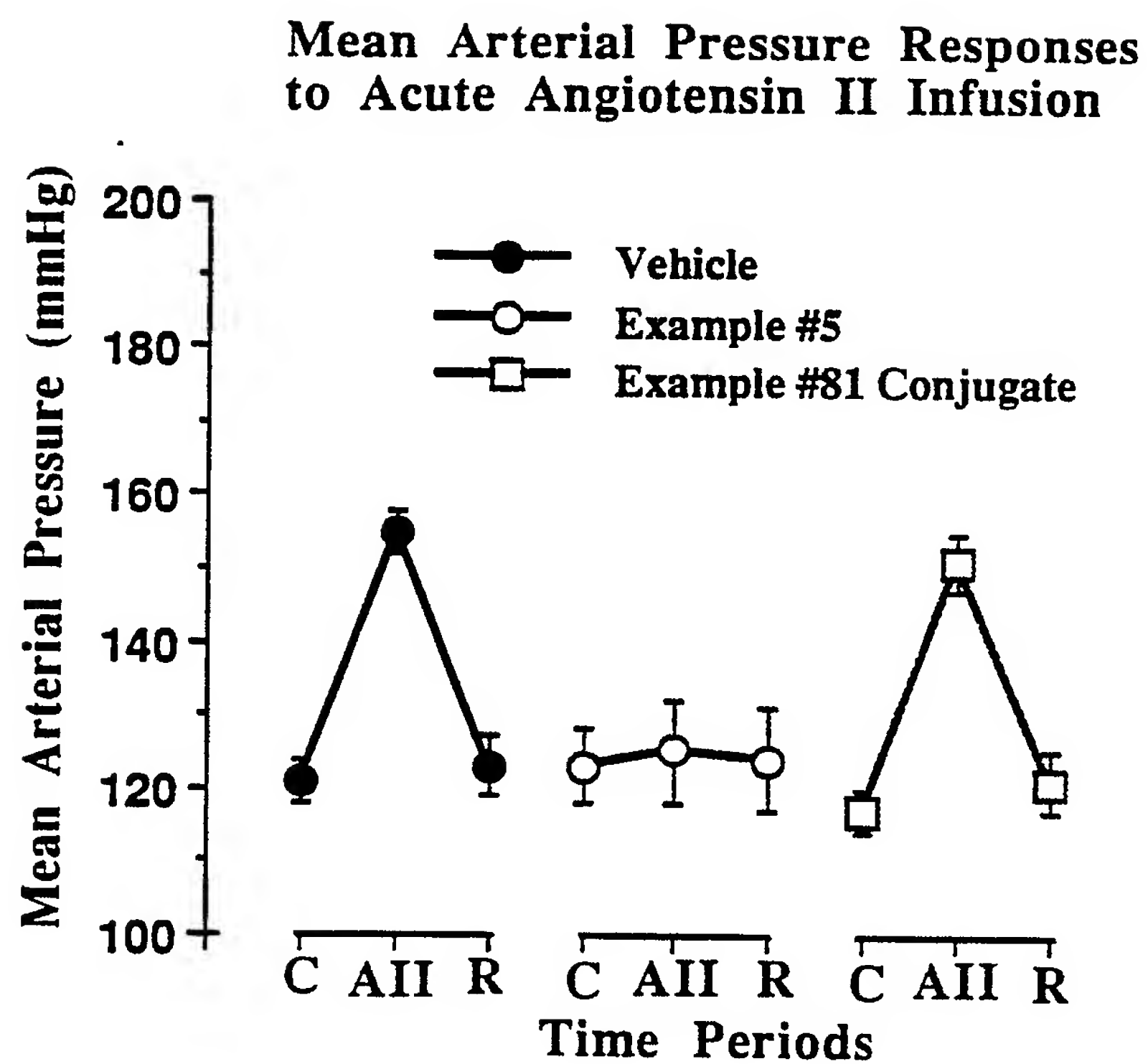


Figure 3

**Figure 4**